CU-catalyzed enantioselective conjugate addition of organometal reagents to unsaturated carbonyls : an enantioselective total synthesis of clavirolide C

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CU-CATALYZED ENANTIOSELECTIVE CONJUGATE ADDITIONS OF ORGANOMETAL REAGENTS TO UNSATURATED CARBONYLS: AN ENANTIOSELECTIVE TOTAL SYNTHESIS OF CLAVIROLIDE C

A Dissertation

By

MICHAEL KEVIN BROWN

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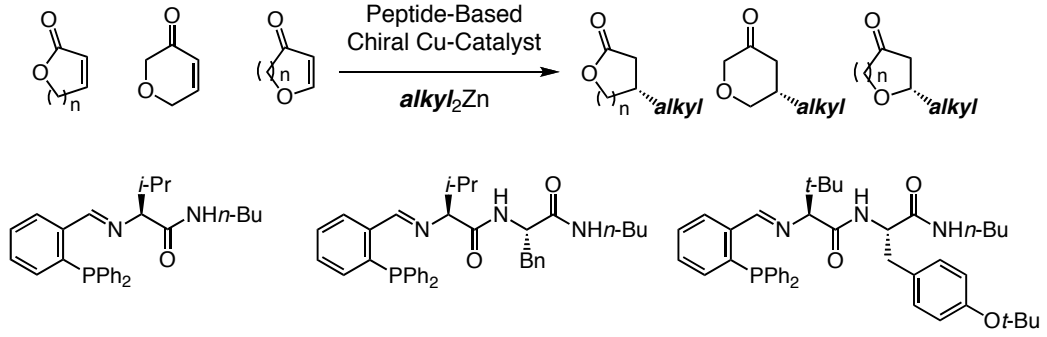
Thesis Advisor: Professor Amir H. Hoveyda

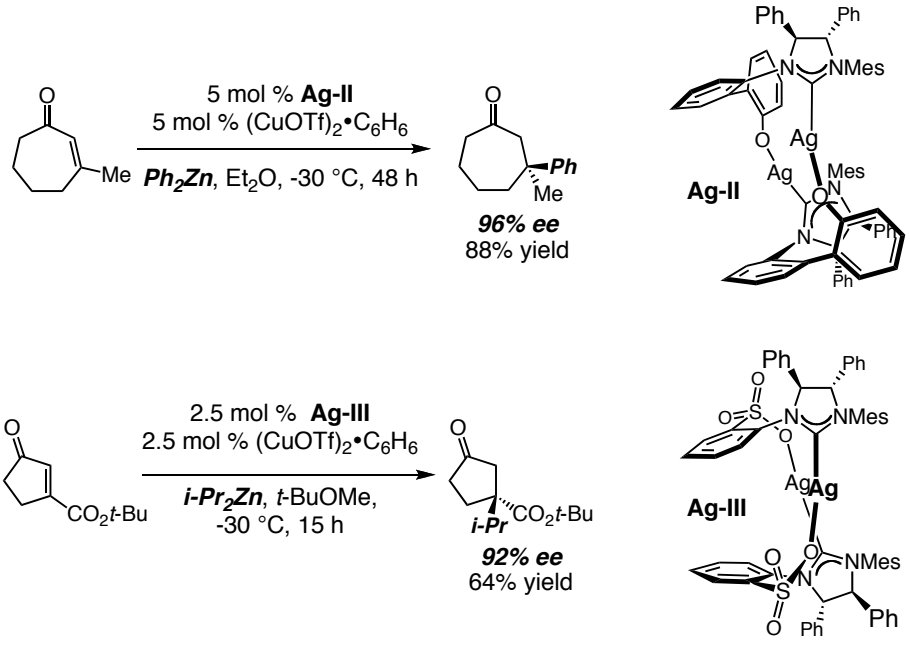
Abstract

■ **Chapter 1.** Methods for highly enantioselective Cu-catalyzed asymmetric conjugate additions of dialkylzinc reagents to unsaturated furanones and pyranones are presented. Transformations are promoted by a chiral peptide-based ligand in the presence of an appropriate Cu-salt. In order to carry out additions to a broad range of substrates, a small family of chiral peptide based ligands was utilized. The synthesis, characterization and use of air-stable Cu-peptide complexes is also presented.



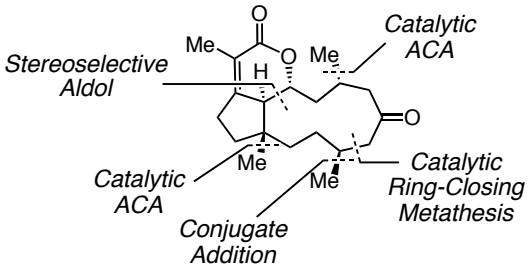
■ **Chapter 2.** New methods for the highly enantioselective formation of all-carbon quaternary stereogenic centers through catalytic asymmetric conjugate additions of dialkyl- as well as diarylzinc reagents are summarized. As introduction to Cu-catalyzed asymmetric conjugate addition to prepared all-carbon quaternary stereogenic centers is

presented. For reactions involving unactivated cyclic β-substituted unsaturated carbonyls, a phenoxy-based *N*-heterocyclic carbene (NHC) ligand was found to optimal. Additions of diorganozinc reagents to cyclic unsaturated γ-ketoesters, however, required the use of a sulfonate-based NHC to provide the desired products efficiently and in high enantiomeric purity. The practicality of the method is demonstrated though the in situ preparation and use of diorganozinc reagents. Representative functionalizations of the enantiomerically enriched enolate are also included.

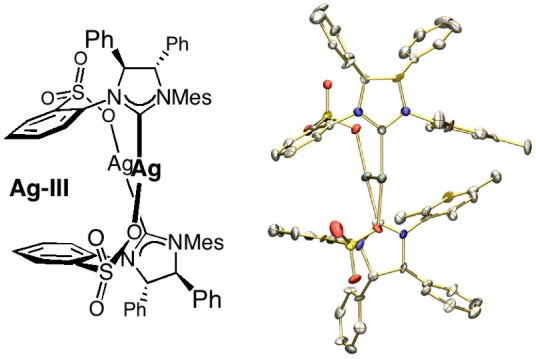


■ **Chapter 3.** An enantioselective total synthesis of diterpenoid natural product clavirolide C is presented. The total synthesis requires 17 steps (longest liner) and provides the target compound in 3.5% overall yield. These studies have led to the development of a new method for the synthesis of all-carbon quaternary stereogenic centers though Cu-catalyzed ACA of trialkylaluminum reagents to β-substituted cyclopentenone derivatives. Additional features of the synthesis include: (i) Cu-catalyzed asymmetric conjugate addition of dimethylzinc to an unsaturated lactone (ii) stereoselective aldol addition between an aliphatic-based aldehyde and a cyclopentenone-

derived enolate (iii) the synthesis of an 11-membered ring though catalytic ring-closing metathesis.



■ **Chapter 4.** Several route for the synthesis of sulfonate-based NHC complexes are presented. In the course of these studies, a new method for the preparation of imidazolinium salts was discovered. Mechanistic studies, carried out to understand the details of the imidazolinium salt formation, eventually led to an improved synthesis. Physical properties of the sulfonate-based NHC are also summarized.



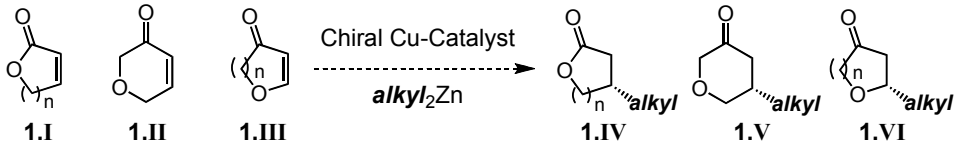
Chapter 1. Highly Enantioselective Cu-Catalyzed Conjugate Additions of Dialkylzinc Reagents to Unsaturated Furanones and Pyranones: Preparation of Air-Stable and Catalytically Active Cu-Peptide Complexes

1.1 *Introduction*

Copper-catalyzed asymmetric conjugate addition (ACA) of alkyl metals to α,β-unsaturated carbonyls has proven to be of notable utility for the stereoselective formation of C-C bonds.[1] Consequently, development of this transformation has been the interest of a number of laboratories. Despite numerous reports on ACA to unsaturated carbonyls,[1] related additions to unsaturated furanones and pyranones (Substrate classes **1.I-1.III)** have received little attention. *Enantioselective conjugate additions of alkylmetals to these substrates produce a class of optically enriched small to medium oxygen-containing rings (**1.IV-1.VI**) that cannot be efficiently accessed by other methods.*

(1) (a) "Recent Advances in Catalytic Enantioselective Michael Additions," N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171-196. (b) "Enantioselective Copper-Catalyzed Conjugate Addition," Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221-3236. (c) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. in *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, pp. 224-258. (d) "Recent Advances in Metal-Catalyzed Asymmetric Conjugate Additions," Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279-1300.

Scheme 1.1: Cu-Catalyzed ACA to Unsaturated Furanones and Pyranones



1.I **1.II** **1.III** **1.IV** **1.V** **1.VI**

1.2 *Background*

Several studies have addressed ACA to unsaturated furanones and pyranones. While high enantioselectivities were observed, generally these methods are limited in substrate and nucleophile scope. The following sections will briefly outline these disclosures.

1.2.a ACA to Unsaturated Lactones (Type 1.I)

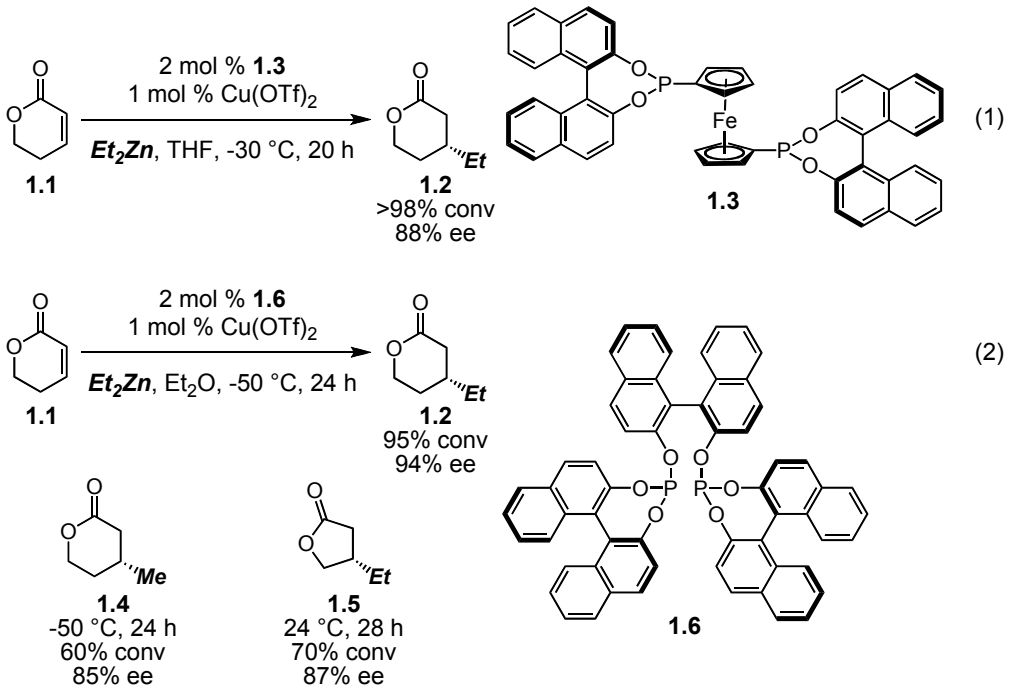
In 2002, Reetz and co-workers disclosed a method for Cu-catalyzed ACA of Et_2Zn to unsaturated lactone **1.1**, promoted by phosphite-based ligand **1.3** (Scheme 1.2, eq (1)).[2] While good enantioselectivity (88% ee) was observed, only a single example was reported. Subsequently, Chan and coworkers reported phosphite-based ligand **1.5**, which efficiently and selectively promoted Cu-catalyzed ACA of dialkylzinc reagents to five- and six-membered ring unsaturated lactones (Scheme 1.2, eq (2)).[3] In spite of high enantioselectivities (85-87% ee), additions with either the less reactive Me_2Zn or with the

(2) "Copper-Catalyzed Enantioselective Conjugate Addition of Diethylzinc to α,β-Unsaturated Carbonyl Compounds Using Diphosphites as Chiral Ligands," Reetz, M. T.; Gosberg, A.; Moulin, D. *Tetrahedron Lett.* **2002**, *43*, 1189-1191.

(3) (a) "Conjugate Addition of Diethylzinc to α,β-Unsaturated Lactones Catalyzed by Copper-Phosphite Complexes," Yan, M.; Zhou, Z. Y.; Chan, A. C. S. *Chem. Commun,* **2000**, 115-116. (b) "Highly Enantioselective 1,4-Conjugate Addition of Dialkylzinc to α,β-Unsaturated Lactone by Diphosphite-Copper Complexes," Liang, L.; Su, L.; Li, X; Chan, A. C. S. *Tetrahedron Lett.* **2003**, *44*, 7217-7220. (c) "Highly Enantioselective Copper-Catalyzed 1,4-Conjugate Addition of Diethylzinc to Cyclic Enones and α,β-Unsaturated Lactones," Liang, L.; Yan, M.; Li, Y. M.; Chan, A. C. S. *Tetrahedron Asym.* **2004**, *15*, 2575-2578.

corresponding five-membered ring unsaturated lactone delivered the product in 60% (**1.4**) and 70% conv (**1.5**), respectively. For reasons that will be clarified later, yield of isolated product was not reported (only % conv or GC yields).

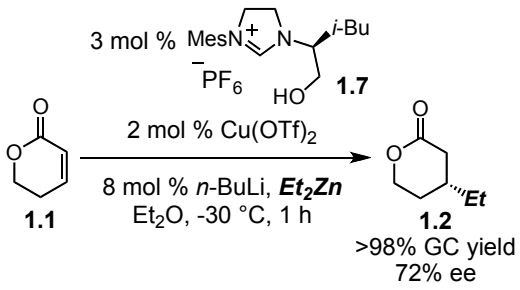
Scheme 1.2: Cu-Catalyzed ACA to Unsaturated Lactones Promoted by Phosphite Based Ligands



Mauduit and coworkers reported a method for Cu-catalyzed ACAs of dialkylzinc reagents to cyclic enones promoted by bidentate *N*-heterocyclic carbene (NHC) precursor **1.7** (Scheme 1.3). In one example, addition to an unsaturated lactone (**1.1**) was reported. While this process was efficient (>98% GC yield, 1 h), moderate enantioselectivity (72% ee) was observed.[4]

(4) "New Bidentate Alkoxy-NHC Ligand for Enantioselective Copper-Catalysed Conjugate Addition," Clavier, H.; Coutable, L.; Cuillenmin, J. C.; Mauduit, M. *Tetrahedron Asym.* **2005**, *16*, 921-924.

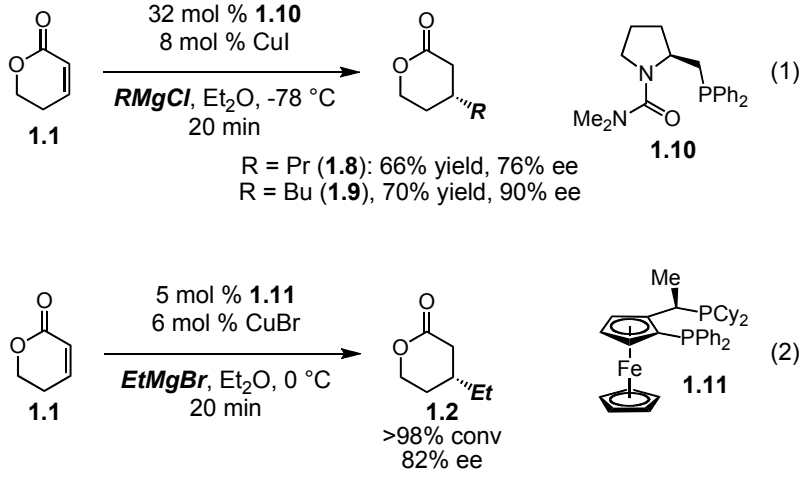
Scheme 1.3: NHC-Cu Promoted ACA of Et_2Zn to **1.1**



While dialkylzinc reagents (utilized in the methods illustrated in Scheme 1.2-1.3) are mild and tolerant of many sensitive functional groups (e.g., alkyl halides and aldehydes), it is difficult to surpass the practicality of Grignard reagents in terms of ease of synthesis and handling. In 1995, Tomioka and coworkers reported a method for Cu-catalyzed ACA of Grignard reagents to unsaturated lactone **1.1** (Scheme 1.4, eq (1)).[5] Remarkably, conjugate addition of *n*-BuMgCl provided **1.9** in significantly higher selectivity (90% ee) when compared to addition of *n*-PrMgCl (76% ee, **1.8**). Furthermore, high catalyst loading (32 mol % **1.10**, 8 mol % CuI) was necessary to achieve optimal enantioselectivities. Subsequently, Feringa and coworkers have reported a method for Cu-catalyzed ACA of Grignard reagents to cyclic enones ((Scheme 1.4, eq (2)).[6] In one instance, ACA of EtMgBr, promoted by **1.11** in combination with CuBr, to unsaturated lactone **1.1** delivered **1.2** in 82% ee (>98% conv).

(5) "Catalytic Asymmetric Conjugate Addition of Grignard Reagents Mediated by Copper(I)-Chiral Bidentate Phosphine Complex," Kanai, M.; Tomioka, K. *Tetrahedron Lett.* **1995**, *36*, 4275-4278.
(6) "Copper-Catalyzed Enantioselective Conjugate Addition of Grignard Reagents to Cyclic Enones," Feringa, B. L.; Badorrey, R.; Peña, D.; Harutyunyan, S. R.; Minnaard, A. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5834-5838.

***Scheme 1.4*:** Cu-Catalyzed ACA of Grignard Reagents to **1.1**



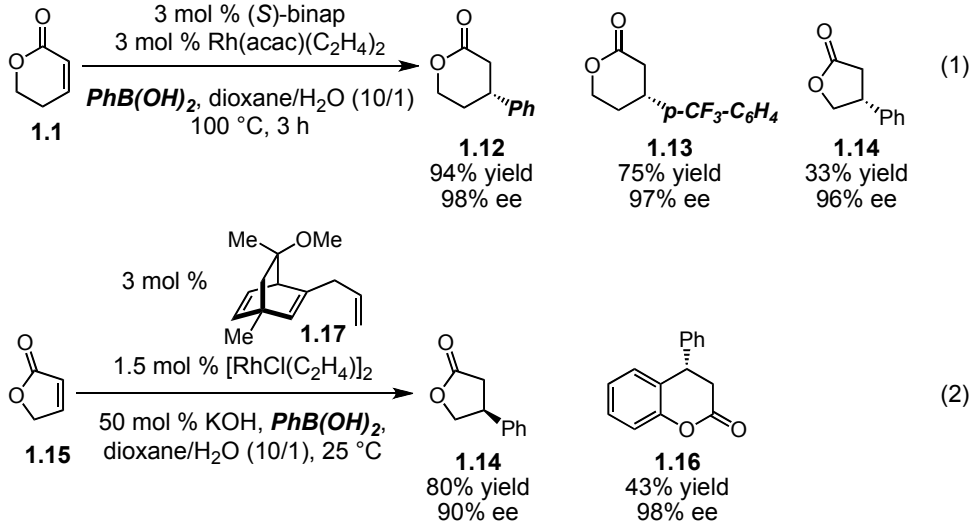
Several methods have been reported to carry out highly enantioselective Rh-catalyzed conjugate addition of arylboronic acids to unsaturated lactones (Scheme 1.5, eq (1)).[7] In 1999, Hayashi and coworkers reported a method for highly enantioselective Rh-catalyzed ACA of a variety of arylboronic acids to unsaturated lactones (**1.1** and **1.15**).[8] While high enantioselectivities were realized for addition to cyclopentenone (**1.15**) and cyclohexenone (**1.1**), low yield of isolated product was observed for the formation of **1.14**. In related studies, Carreira and coworkers have demonstrated that chiral diene-

(7) For select recent examples of Rh-catalyzed ACA of aryl groups to unsaturated lactones, see: (a) "BINOL-Based Diphosphonites as Ligands in the Asymmetric Rh-Catalyzed Conjugate Addition of Arylboronic Acids," Reetz, M. T.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *3*, 4083-4085. (b) "Enantiomerically Pure Rhodium Complexes Bearing 1,5-Diphenyl-1,5-cyclooctadiene as a Chiral Diene Ligand. Their Use as Catalysts for Asymmetric 1,4-Addition of Phenylzinc Chloride," Kina, A.; Ueyama, K.; Hayashi, T. *Org. Lett.* **2005**, *7*, 5889-5892. (c) "Preparation of C_2-Symmetric Bicyclo[2.2.2]octa-2,5-diene Ligands and Their Use for Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids," Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503-2508. (d) "A Chiral Bis-Sulfoxide Ligand in Late-Transition Metal Catalysis: Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids to Electron Deficient Olefins," Mariz, R.; Luan, X.; Gatti, M.; Lindin, A.; Dorta, R. *J. Am. Chem. Soc.* **2008**, *130*, 2172-2173.

(8) "Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboron Reagents to α,β-Unsaturated Esters," Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron Asymmetry.* **1999**, *10*, 4047-4056.

based ligand **1.17** was an efficient and selective (90% ee) catalyst for ACA to five-membered ring unsaturated lactone **1.15** as well as coumarin (Scheme 1.5, eq (2)).[9]

Scheme 1.5: Rh-Catalyzed ACA of Arylboronic Acids to Unsaturated Lactones

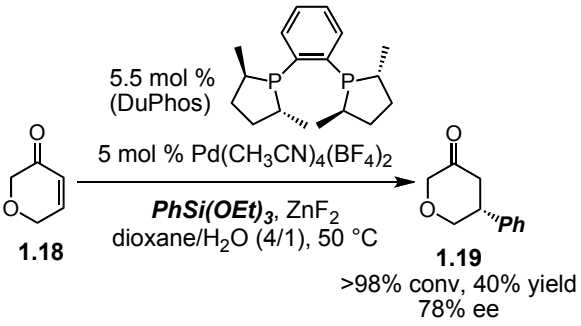


1.2.b ACA to 3-Oxycyclohexenones (Type 1.II)

In 2007, Feringa and coworkers reported a method for Pd-catalyzed ACA of arylsiloxanes to cyclic enones (Scheme 1.6).[10] In a single instance, ACA to 3-oxycyclohexenone **1.18** was carried out. While moderate enantioselectivity (78% ee) and yield (40% yield) were observed, this was the only reported example for the addition of any organometal reagent to this substrate class.

(9) "Chiral [2.2.2] Dienes as Ligands for Rh(I) in Conjugate Additions of Boronic Acids to a Wide Range of Acceptors," Defieber, C.; Paquin, J. F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873-3876.
(10) "Enantioselective Palladium-Catalyzed Conjugate Addition of Arylsiloxanes," Gini, F.; Hessen, B.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2007**, 710-712.

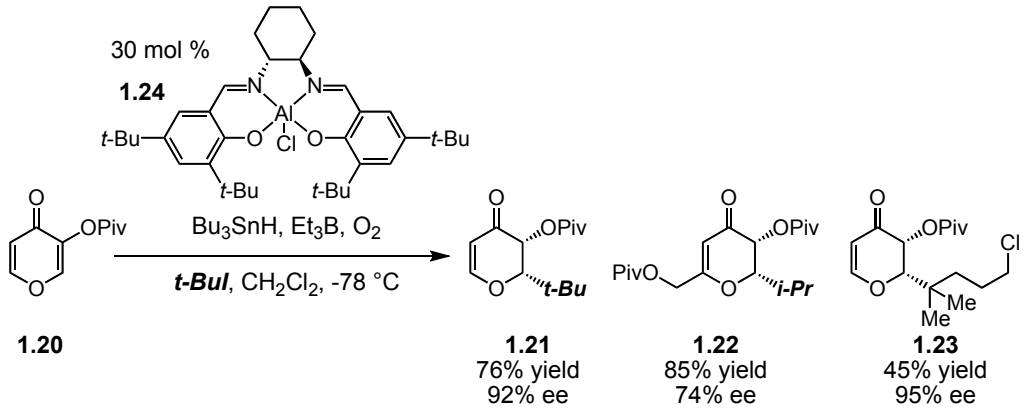
Scheme 1.6: Pd-Catalyzed ACA of Arylsiloxanes to **1.18**



1.2.c ACA to Cyclic Vinylogous Esters (Type 1.III)

As illustrated in Scheme 1.7, enantioselective radical additions of alkyl iodides to acyloxy pyrones (**1.20**) have been carried out by Sibi and coworkers.[11] While high enantioselectivities were observed for additions of sterically hindered alkyl groups (*t*-Bu, $(CH_3)_2C(CH_2)_3Cl$), reactions with less sterically hindered iodides provided the products with decreased levels of enantioselectivity (i.e., synthesis of **1.22**). Furthermore, high catalyst loadings (30 mol%) were required to achieve efficient reaction.

Scheme 1.7: Enantioselective Radical Additions to Acyloxy Pyrones



(11) "Pyrones to Pyrans: Enantioselective Radical Additions to Acyloxy Pyrones," Sibi, M. P.; Zimmerman, J. *J. Am. Chem. Soc.* **2006**, *128*, 13346-13347.

1.3 *Cu-Catalyzed ACA Reactions with Dialkylzinc Reagents Promoted by Chiral Amino Acid-Derived Phosphine Ligands*

In our group, we have taken interest in solving problems in ACA that are either unique or inefficient with existing catalytic systems. Each of the systems developed in our group has benefited from the modular nature of the amino acid-based chiral ligands (i.e., **1.32**, Scheme 1.8), allowing us to develop an optimal chiral ligand for each substrate class studied. This section will briefly outline these reports.[12,13]

Early success was realized with the discovery that amino acid-based chiral phosphine **1.32**, in combination with $(CuOTf)_2 \bullet C_6H_6$, promoted highly enantioselective (>95% ee) and efficient ACAs of dialkylzinc reagents to cyclic enones (Scheme 1.8).[14] One of the noteworthy aspects of this study is that ACAs to cyclopentenones (i.e. **1.25**) could be carried out with high efficiency and selectivity (97-98% ee). In general, reported methods for Cu-catalyzed ACA to cyclopentenone derivatives suffer from low efficiency and selectivity.[15] Cu-catalyzed ACA of *i*-Pr_2Zn, however, in the presence of **1.32**, provided **1.30** and **1.31** with moderate selectivities (72% and 62% ee, respectively).

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(12) "Small Peptides as Ligands for Catalytic Asymmetric Alkylations of Olefins. Rational Design of Catalysts or of Searches that Lead to Them?," Hoveyda, A. H.; Hird, A. W.; Kacpryzynski, M. A. *Chem. Commun.* **2004**, 1779-1785.

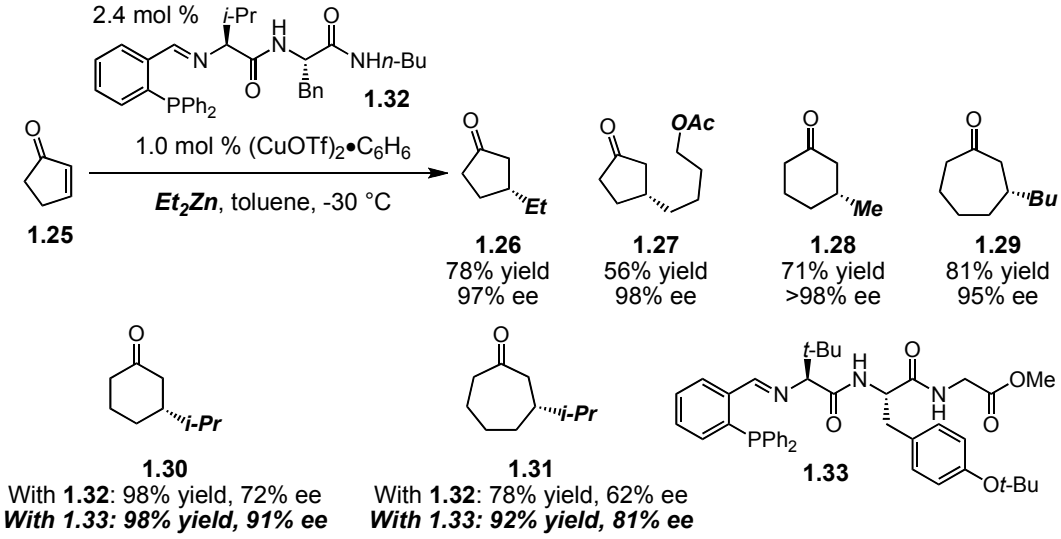
(13) For a discussion regarding combinatorial screening strategies, see: "High-Throughput Strategies for the Discovery of Catalysts," Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem. Eur. J.* **1998**, *4*, 1885-1889.

(14) "Modular Peptide-Based Phosphine Ligands in Asymmetric Catalysis: Efficient and Enantioselective Cu-Catalyzed Additions to Five-, Six-, and Seven-Membered Cyclic Enones," Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755-756.

(15) Cu-catalyzed ACA to cyclopentenone derived substrates are more challenging. For examples, see: (a) "New Chiral Oxazoline-Phosphite Ligands for the Enantioselective Copper-Catalyzed 1,4-Addition of Organozinc Reagents to Enones," Escher, I. H.; Pfaltz, A. *Tetrahedron* **2000**, *56*, 2879-2888. (b) "Enantioselective 1,4-Addition of Diorganozinc Reagents to Cyclic Enones Using Chiral Diphosphite Ligands Derived from H_8-Binaphthol," Liand, L.; Au-Yeung, T. T.-L.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 3799-3801. (c) ref (14).

Here the modular nature of the chiral ligand proved crucial as, after screening ~40 ligand candidates (prepared on solid support),[13] chiral phosphine **1.33**, bearing *t*-Leu and Tyr(O*t*-Bu) residues, was discovered to provide the products (**1.30**-**1.31**) in synthetically useful levels of enantioselectivities (81-91% ee).

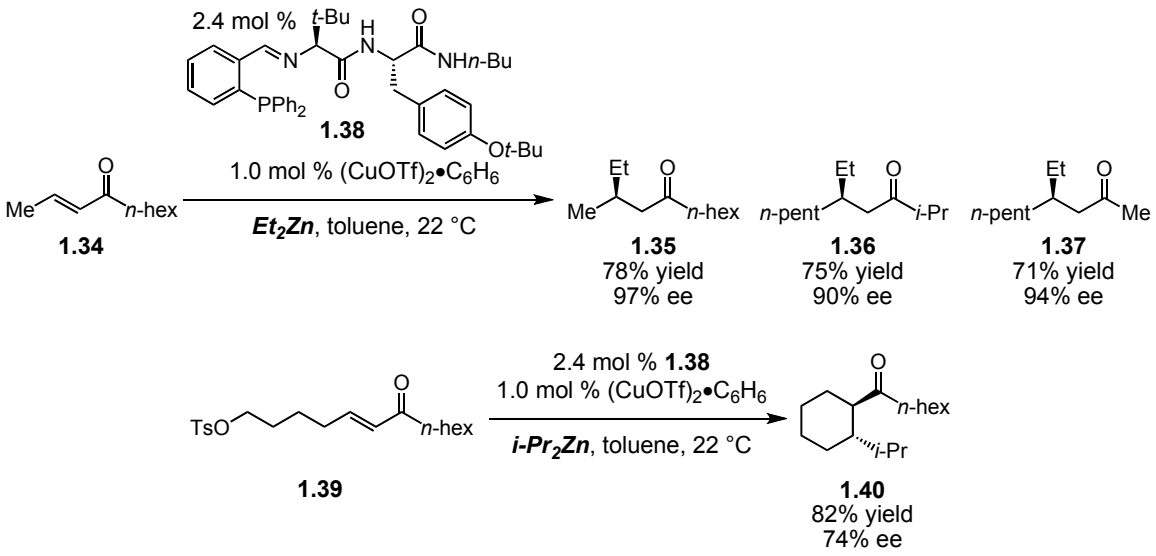
Scheme 1.8: Cu-Catalyzed ACA of Dialkylzinc Reagents to Cyclic Enones



Subsequently, we have demonstrated that highly enantioselective additions to acyclic aliphatic enones (i.e. **1.34**) can be achieved by the use of related chiral amino acid-based ligand **1.38** (Scheme 1.9).[16] ACA to substrates bearing an -OTs group led to formation of the cyclohexane derivative **1.40** in high yield (82%) and enantioselectivity (74% ee);[17] however, as illustrated with the example provided, ACAs of *i*-Pr_2Zn are less selective (74% ee) than reaction with Et_2Zn or Me_2Zn (90-97% ee).

(16) "Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Acyclic Aliphatic Enones," Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779-781.
(17) The moderate enantioselectivity observed in this case is not an artifact of the –OTs unit. Related reactions with Et_2Zn, furnish the desired product in high enantioselectivity (95% ee).

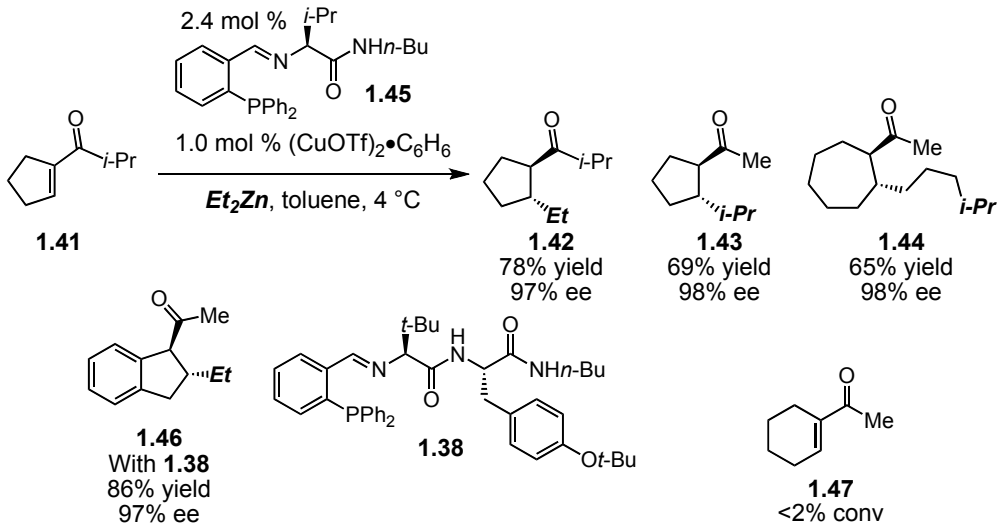
Scheme 1.9: Cu-Catalyzed ACA to Acyclic Aliphatic Enones



For additions to more highly substituted enones, such as **1.41**, amino acid-based ligand **1.45**, which bears a single amino acid residue, was discovered to be optimal (Scheme 1.10).[18] Highly enantioselective additions of dialkylzinc reagents were carried out to both the five- and seven-membered ring trisubstituted enones; however, under a variety of conditions, reactions with six-membered ring enone **1.47** led to <2% conv. The product derived from addition to **1.47** could be obtained through the route illustrated in Scheme 1.9 (i.e., conversion of **1.39** to **1.40**). Enantioselective synthesis of **1.46** required the use of dipeptide **1.38** to achieve high yield (86%); the identical reaction, promoted by **1.45**, provided **1.42** in 95% ee accompanied with ~40% of an unidentified byproduct.

(18) "Efficient Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzincs to Trisubstituted Cyclic Enones," Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362-13363.

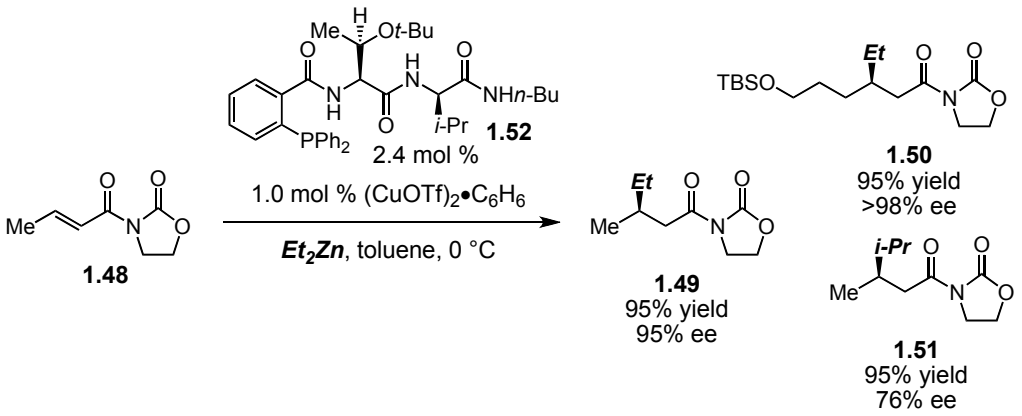
Scheme 1.10: Cu-Catalyzed ACA to Trisubstituted Cyclic Enones



Cu-catalyzed ACAs of dialkylzinc reagents to *N*-acyloxazolidinones (i.e., **1.48**), promoted by chiral Schiff base derived ligands such as **1.38**, provided the products (e.g., **1.49**) in moderate to low enantioselectivity (<75% ee).[19] After extensive screening, chiral triamide ligand **1.52**, bearing L- and D-amino acid residues was discovered to be optimal (Scheme 1.11). The products, **1.49**-**1.51**, derived from additions of a variety of dialkylzinc reagents, were generated efficiently and in high enantioselectivity (76%->98% ee). Furthermore, lending to the synthetic versatility of the oxazolidinone unit, conversion to Weinreb amide or carboxylic acid derivatives was carried out in high yield (>80% yield).

(19) "Cu-Catalyzed Enantioselective Conjugate Additions of Alkyl Zinc Reagents to Unsaturated *N*-Acyloxazolidinones Promoted by a Chiral Triamide Phosphane," Hird, A. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276-1279

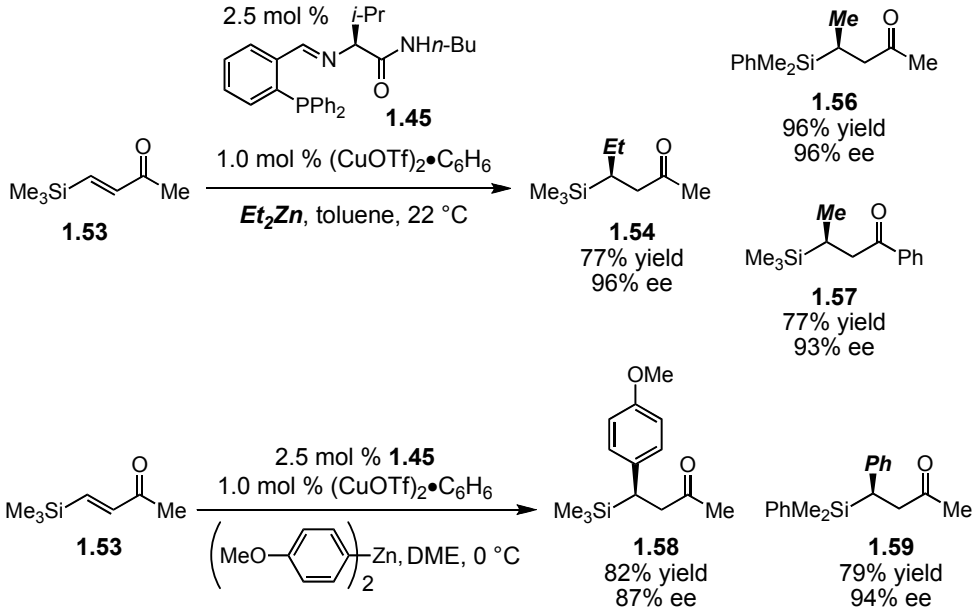
Scheme 1.11: Cu-Catalyzed ACA to *N*-Acyloxazolidinones



Mono amino acid-based ligand **1.45** was discovered to be an efficient ligand for additions to β-silyl unsaturated ketones (i.e. **1.53**, Scheme 1.12).[20,21] While highly enantioselective (93-97% ee) additions of Me_2Zn and Et_2Zn were carried out, reactions involving longer chain or sterically hindered dialkylzinc reagents (e.g., Bu_2Zn or *i*-Pr_2Zn, respectively) were inefficient (<2% conv). Furthermore, for the first time in our laboratories, highly selective additions of diarylzinc reagents, promoted by peptide-based ligands, were realized (87-94% ee). To reduce uncatalyzed addition of the diarylzinc reagent to **1.53**, we sought to disfavor coordination of the zinc reagent to the Lewis basic carbonyl of **1.53** by carrying out the reaction in coordinating solvents (reactions in toluene were efficient yet non-selective: <50% ee). These studies led to the discovery that reactions carried out in DME provided **1.58** and **1.59** in high enantioselectivities (87% and 94% ee, respectively).

(20) "Cu-Catalyzed Asymmetric Conjugate Additions of Dialkyl- and Diarylzinc Reagents to Acyclic β-Silyl-α,β-Unsaturated Ketone. Synthesis of Allylsilanes in High Diastereo- and Enantiomeric Purity," Kacprzynski, M. A.; Kazane, S. A.; May, T. L.; Hoveyda, A. H. *Org. Lett.* **2007**, *9*, 3187-3190.
(21) The utility of β-silyl carbonyls is well established: Fleming, I. *Science of Synthesis*; Thieme: Stuttgart, Germany, 2002: Vol. 4: pp 927-946.

Scheme 1.12: Cu-Catalyzed ACA to β-Silyl Unsaturated Ketones



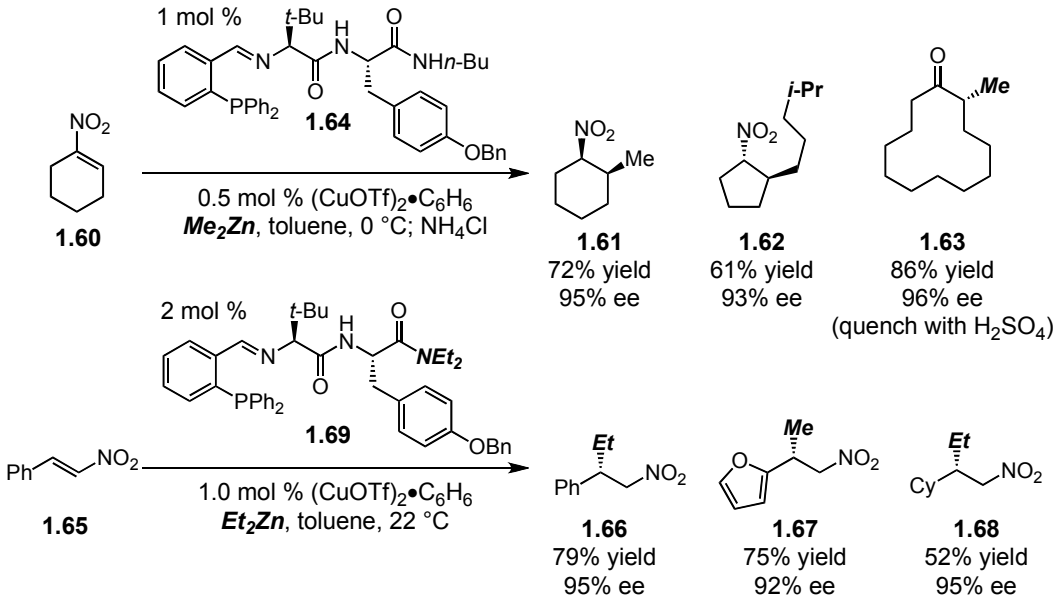
This class of peptide-based ligands has also proven to be effective for promoting Cu-catalyzed ACA of dialkylzinc reagents to nitroalkenes (i.e., **1.60**).[22] As illustrated in Scheme 1.13, highly enantioselective additions (93%-96% ee) to five-, six-, seven-, as well as 12-membered ring nitroalkene derivatives can be carried out.[22a] When the reactions were quenched with mild acid (NH_4Cl) the nitroalkane products were obtained in good yields (61-89%, **1.61** and **1.62**)). Alternatively, in situ Nef reactions can be carried out to provide the cyclic ketone product, such as **1.63**, when the reactions were quenched with strong acid (H_2SO_4).

Additions to acyclic nitroalkenes (i.e., **1.65**) required the use of a chiral peptide-based ligand bearing an $–NEt_2$ terminus (**1.69**) (vs. –NHBu in **1.64**) to achieve high

(22) (a) "Cu-Catalyzed Enantioselective Conjugate Addtion of Alkylzincs to Cyclic Nitroalkenes: Catalytic Asymmetric Synthesis of Cyclic α-Substituted Ketones," Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192-8193. (b) "Efficient Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Aromatic and Aliphatic Acyclic Nitroalkenes," Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2002**, *6*, 2829-2832.

enantioselectivities (92-95% ee, Scheme 1.13).[22b] For example, Cu-catalyzed ACA promoted to **1.65** by 2 mol % **1.64** and 1 mol % $(CuOTf)_2 \bullet C_6H_6$ delivered **1.66** in 82% ee (vs. 95% ee with **1.69**). High efficiency and enantioselectivities (92-95% ee) were observed regardless of the β-substituent (electronically modified aryl, heteroaryl, as well as alkyl).

Scheme 1.13: Cu-Catalyzed ACA to Nitroalkenes

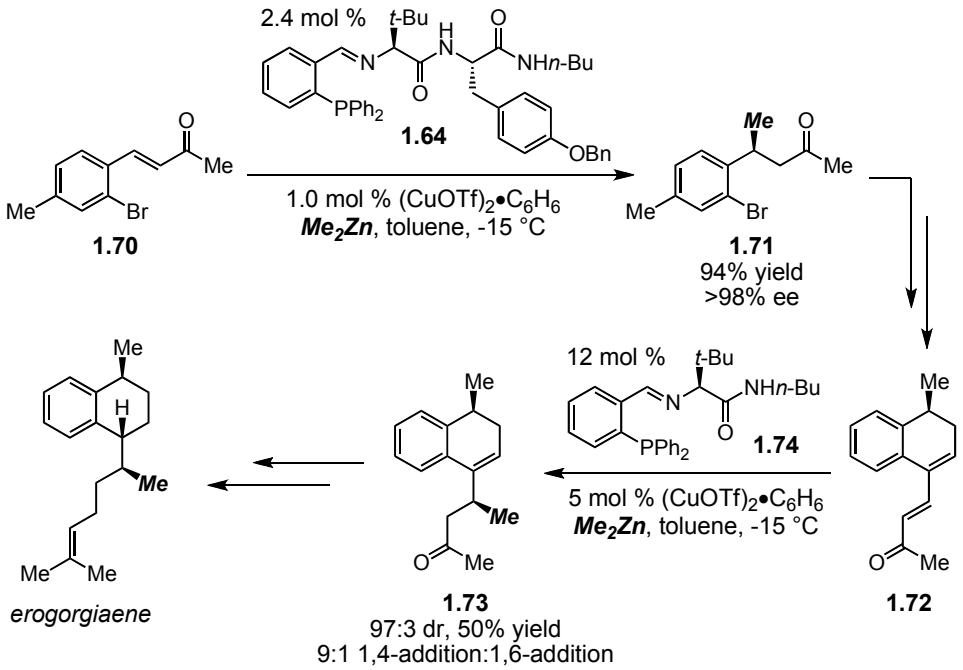


The utility of the above Cu-catalyzed ACA protocols was demonstrated by an efficient and enantioselective total synthesis of erogorgiaene (Scheme 1.14).[23] For each ACA transformation, a different chiral amino acid-based ligand was discovered to be optimal, thus highlighting the need for a small family of chiral catalysts. It is important to note that chiral ligand **1.74** controls not only the diastereoselectivity of the conjugate

(23) "Enantioselective Total Synthesis of Erogorgiaene: Application of Asymmetric Cu-Catalyzed Conjugate Additions of Alkylzincs to Acyclic Enones," Cesati, R. R. III; de Armas, J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 96-101.

addition process of enone **1.72**, but also the regioselectivity (9:1 1,4-addition:1,6-addition). Cu-catalyzed ACA to **1.72**, promoted by dipeptide **1.64**, provided the desired product in high enantioselectivity (92% ee) but with low regioselectivity (1.5:1 1,4-addition:1,6-addition).

Scheme 1.14: Enantioselective Total Synthesis of Erogorgiaene

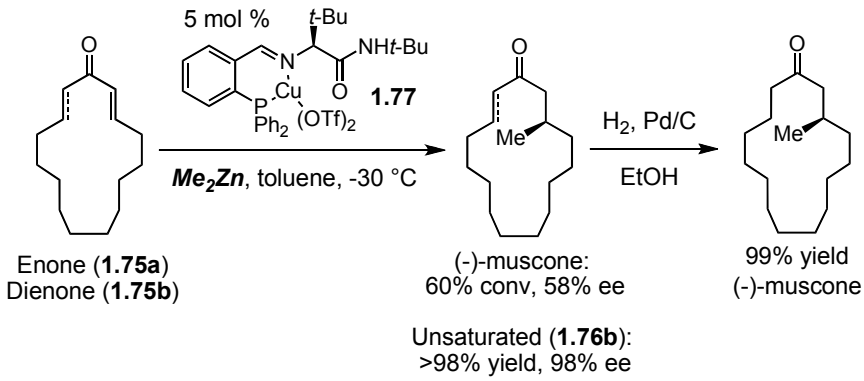


In 2006, Pfaltz and coworkers reported an enantioselective total synthesis of (-)-muscone featuring Cu-catalyzed ACA with peptide-based ligands (Scheme 1.15).[24] It was discovered that ACA of Me_2Zn to mono-enone 14-membered ring substrate **1.75a**, promoted by preformed Cu-complex **1.77**, provided (-)-muscone in 58% ee (60% conv). The researchers suspected that low selectivities observed were due to the flexibility of the macrocyclic enone structure. Therefore, dienone **1.75b** was prepared with the hope that

(24) "Enantioselective Routes to (-)-Muscone," Bulic, B.; Lücking, U.; Pfaltz, A. *Synlett*, **2006**, *7*, 1031-1034.

additional sp^2 carbons would rigidify the structure. Indeed, Cu-catalyzed ACA of **1.75b**, promoted by Cu-complex **1.77**, provided **1.76b** in 98% ee and 98% yield after purification. Hydrogenation of the enone provided (-)-muscone in 99% yield.

Scheme 1.15: Enantioselective Total Synthesis of (-)-Muscone



Recently, our laboratory has taken an interest in Cu-catalyzed ACA of organometal reagents to furnish all-carbon quaternary stereogenic centers (Scheme 1.16).[25,26] Early studies established that Cu-catalyzed ACA of dialkylzinc reagents to β-methyl cyclohexenone under a variety of conditions with peptide-based ligands (e.g., **1.32**) led to low conversions of substrate. Subsequent studies established that additional activation of the enone by installation of an α-ester unit (i.e., **1.78**) was required to achieve high efficiency with reactions promoted by peptide-based ligands; however, it was not until the discovery of chiral anthranilic acid dipeptide-based ligand **1.82** that high

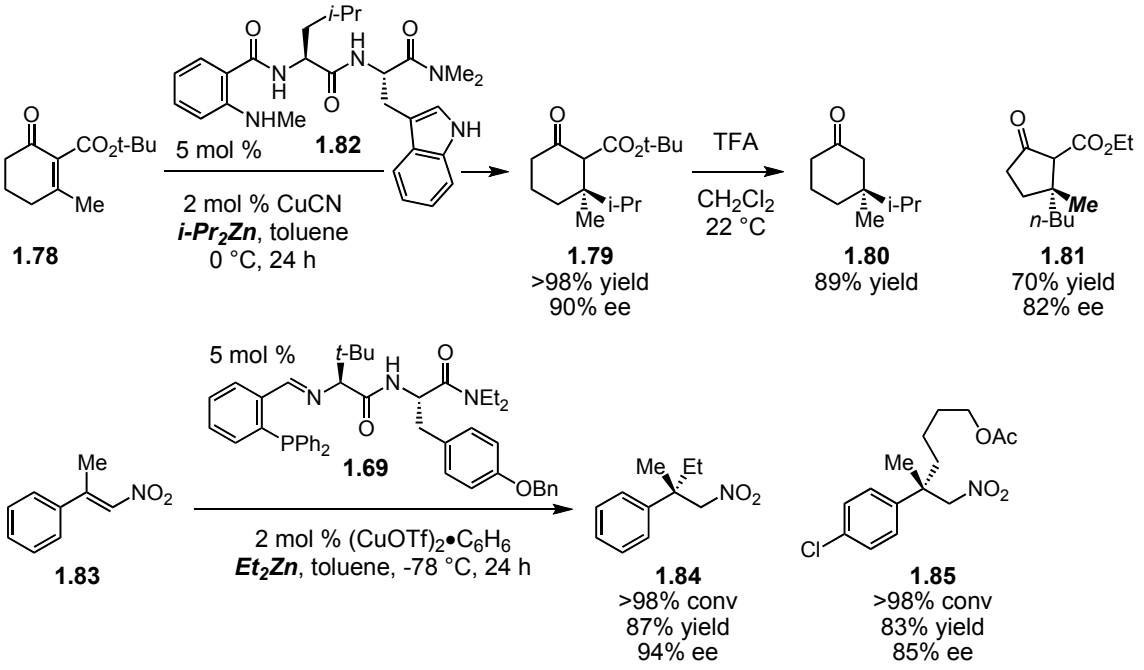
(25) (a) "Stereoselective Formation of Quaternary Carbon Centers and Related Functions," Denissova, I.; Barriault, L. *Tetrahedron*, **2003**, *59*, 10105-10146. (b) "Asymmetric Catalysis Special Feature Part I: Catalytic Asymmetric Synthesis of All-Carbon Quaternary Stereocenters," Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363-5367. (c) J. Christophers, A. Baro (Eds.), *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis,* Wiley-VCH, Weinheim, **2006**.
(26) For a full discussion of the methods illustrated in Scheme 1.16, as well as related reactions to prepare all-carbon quaternary stereogenic centers by Cu-catalyzed ACAs, see: Chapter 2

selectivities were realized.[27] Additions of a variety of dialkylzinc reagents, including the sterically hindered *i*-Pr_2Zn and the less reactive Me_2Zn, can be carried out with high selectivity to both the five- and six-membered ring enones (formation of **1.79** and **1.81**). The ester unit could be efficiently cleaved by treatment with TFA to provide **1.80** in 89% yield.

In separate studies it was discovered that Cu-catalyzed ACA to highly activated tri-substituted nitroalkenes could be carried out with chiral phosphine **1.69** (Scheme 1.16).[28] Highly enantioselective (85-94% ee) and efficient additions of Et_2Zn, Bu_2Zn, as well as an acetate-containing dialkylzinc reagent to β-aryl-β-methyl nitroalkenes was achieved.

(27) "Catalytic Enantioselective Alkylations of Tetrasubstituted Olefins. Synthesis of All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Enones," Hird. A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988-14989.
(28) "Enantioselective Synthesis of Nitroalkanes Bearing All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Additions," Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584-4585.

Scheme 1.16: Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers by Cu-Catalyzed ACA.



1.4 *Cu-Catalyzed Enantioselective Conjugate Additions of Dialkylzinc Reagents to Unsaturated Furanones and Pyranones*[29]

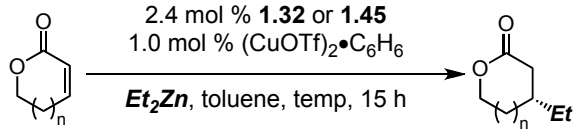
1.4.a Cu-Catalyzed ACA to Unsaturated Lactones

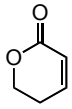
Initial studies indicated that under a variety of conditions, ACA of Et_2Zn to lactone **1.1**, promoted by peptide based ligands **1.45** and **1.32** in combination with $(CuOTf)_2•C_6H_6$, consistently resulted in high conversion (70->98%) and selectivities (>96% ee) but with low GC yields (<25%) (Table 1.1). Addition to five-membered ring

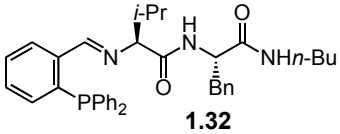
(29) "Highly Enantioselective Cu-Catalyzed Conjugate Additions of Dialkylzinc Reagents to Unsaturated Furanones and Pyranones: Preparation of Air-Stable and Catalytically Active Cu-Peptide Complexes," Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306-5310.

substrate **1.15** provided the desired product in low GC yield (<5%) and selectivity (45% ee).

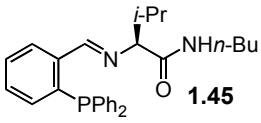
Table 1.1: Initial Survey of Chiral Ligands and Conditions



entry		ligand	temp (°C)	conv (%)	***GC yield (%)***	ee (%)
1		**1.32**	-30	97	***18***	96
2		**1.45**	-30	>98	***20***	96
3		**1.45**	-40	96	***24***	92
4	**1.1**	**1.45**	-78	70	***<2***	--
5	 **1.15**	**1.32**	-30	77	***<5***	45



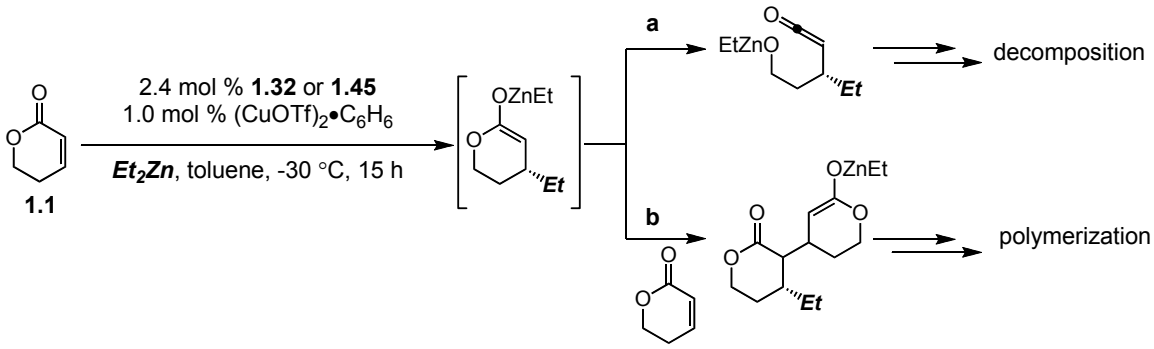
1.32



1.45

Two possible rationales could account for the low GC yields (Scheme 1.17): (1) The zinc-enolate may decompose to a ketene that may then undergo other side-reactions (path **a**), or (2) the zinc-enolate may undergo subsequent Michael reaction with another substrate giving rise to polymer (path **b**). Regardless, we surmised that a rapid internal trap of the zinc-enolate might circumvent these problems.

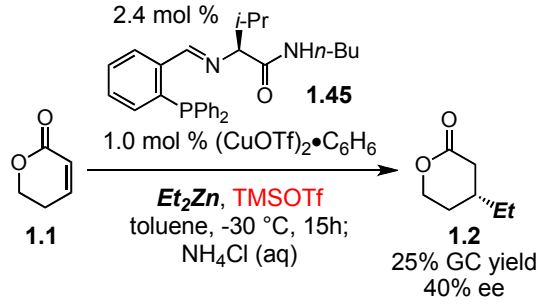
Scheme 1.17: Possible Decomposition Pathways of the Generated Zinc-Enolate



Several points must be considered when choosing a suitable trapping reagent: (1) since it is necessary that the trapping reagent be present in the reaction mixture from the onset, it must be compatible with the dialkylzinc reagent. (2) The trapping reagent should not interfere with the catalytic process, a consequence that might reduce enantioselectivity and/or efficiency. (3) The product obtained from in situ trapping, before aqueous workup, must be stable under the reaction conditions.

The first trapping reagent we imagined that might fit the above criteria was TMSOTf; however, under these conditions, Cu-catalyzed ACA of Et_2Zn to lactone **1.1** provided the desired product in low enantioselectivity (40% ee) and 25% yield (Scheme 1.18). It is likely that due to the highly Lewis acidic nature of TMSOTf, uncatalyzed (non-selective) conjugate addition of Et_2Zn reduced the overall enantioselectivity of the process. Therefore, an alternative strategy was pursued in which the ACA reaction was carried out in the presence of an aldehyde.

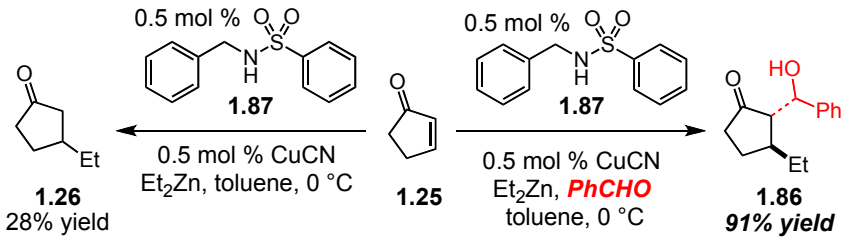
Scheme 1.18: Internal Trap of the Generated Zinc-Enolate with TMSOTf



As illustrated in Scheme 1.19, Noyori and coworkers reported that Cu-catalyzed conjugate addition of Et_2Zn to cyclopentenone **1.25** promoted by sulfonamide **1.87**, provided **1.26** in low yield of isolated product (28%) due to the generated zinc-enolate

undergoing Michael addition with **1.25**.[30] To increase yield of isolated product, PhCHO was introduced into the reaction mixture, such that the zinc enolate would undergo aldol addition prior to undergoing undesired side-reactions. Accordingly, β-hydroxy ketone **1.86** was delivered in 91% yield from this three-component process.[31]

Scheme 1.19: Cu-Catalyzed Conjugate Addition of Dialkylzinc Reagents in the Presence of PhCHO: Noyori

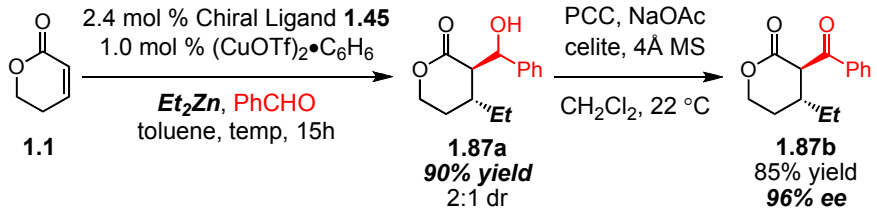


Similarities between Noyori's observation and our studies, prompted us to carry out the conjugate addition in the presence of an aldehyde. Indeed, introduction of PhCHO to the reaction mixture led to the formation of β-hydroxy carbonyl **1.87a** in 90% yield and 96% ee (Scheme 1.20). For purposes of enantiomeric excess determination, **1.87a** was oxidized to provide **1.87b** in 85% yield as a single diastereomer.

(30) "Conjugate Addition of Diorganozinc to α,β-Unsaturated Ketones Catalyzed by a Copper(I)-Sulfonamide Combined System," Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Tetrahedron Lett.* **1996**, *37*, 5141-5144.

(31) For related three component Cu-catalyzed conjugate addition/aldol, see: (a) "Unexpected Enhancement of Enantioselectivity in Copper(II) Catalyzed Conjugate Addition of Diethylzinc to Cyclic Enones with Novel TADDOL Phosphorus Amidite Ligands," Keller, E.; Maurer, J.; Naasz, R.; Schader, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron Asymmetry* **1998**, *9*, 2409-2413. (b) "Highly Enantioselective Catalytic Conjugate Addition and Tandem Conjugate Addition-Aldol Reactions of Organozinc Reagents," Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2620-2623. (c) "Catalytic Enantioselective Synthesis of Prostaglandin E_1 Methyl Ester Using a Tandem 1,4-Addition-Aldol Reaction to a Cyclopenten-3,5-dione Monoacetal," Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841-5842.

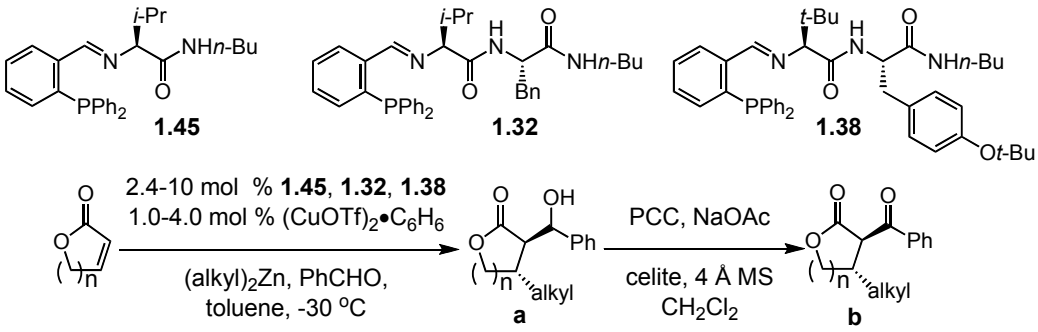
Scheme 1.20: Cu-Catalyzed ACA to Unsaturated Lactone in the Presence of PhCHO

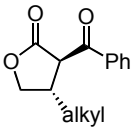
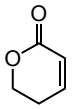
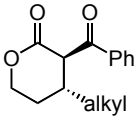
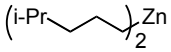
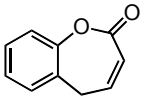
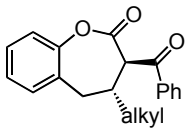


Results for Cu-Catalyzed ACA of dialkylzinc reagents to unsaturated lactones utilizing this three-component method are summarized in Table 1.2. Several points regarding ACA to unsaturated lactones **1.1**, **1.15** and **1.88**[32] are worthy of mention: (1) addition of a variety of dialkylzinc reagents to the five- six- and seven-membered ring lactones are efficiently and selectively (89->98% ee) promoted by $(CuOTf)_2 \bullet C_6H_6$ and previously reported chiral ligands **1.32**, **1.38** and **1.45**. (2) These studies pointed toward a chiral ligand hierarchy. Generally, if reactions promoted by the simplest phosphine (**1.45)** were sluggish, the more potent dipeptide **1.32** was employed (i.e. ACA of Me_2Zn to **1.88** promoted by 10 mol % **1.45** and 4 mol % $(CuOTf)_2 \bullet C_6H_6$ resulted in <2% conv; compare entries 13 and 14, Table 1.2). If less than desirable selectivities were observed, dipeptide **1.38**, bearing a Tle residue, was utilized (e.g., ACA of Et_2Zn to **1.15** promoted by 10 mol % **1.32** and 4 mol % $(CuOTf)_2 \bullet C_6H_6$ resulted in 84% ee; compare entries 3 and 4, Table 1.2).[33] (3) Reactions with the less reactive Me_2Zn were generally inefficient (entries 1 and 7, Table 1.2).

(32) Unsaturated lactone **1.88** was readily prepared by ring-closing metathesis. "Ruthenium Carbene Complexes with *N,N'*-Bis(mesityl)imidazol-2-ylidene Ligands: RCM Catalysts of Extended Scope," Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H. J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204-2207.
(33) See the Experimentals section for more details.

Table 1.2: Cu-Catalyzed ACA of Dialkylzinc Reagents to Unsaturated Lactones[a]

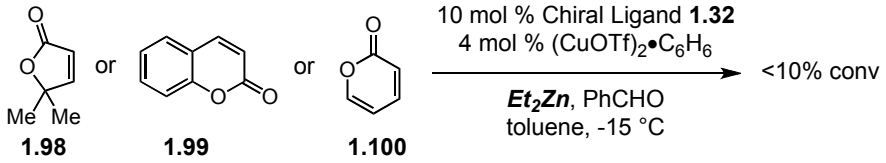


entry	substrate	$(alkyl)_2Zn$	product (after oxidation)		Ligand (mol %)	mol % Cu salt	time (h)	yield (%)[b]	ee (%)[c]
1	 **1.15**	Me_2Zn		**1.89b**	**1.32** (10)	4	48	<2[d]	--
2		Et_2Zn		**1.90b**	**1.45** (20)	8	48	<10	--
3		Et_2Zn		**1.90b**	**1.32** (10)	4	48	58	84
4		Et_2Zn		**1.90b**	**1.38** (10)	4	48	***67***	***97***
5		*i*-Pr_2Zn		**1.91b**	**1.32** (10)	4	48	***85***	***89***
6		*i*-Pr_2Zn		**1.91b**	**1.38** (10)	4	48	90	83
7	 **1.1**	Me_2Zn		**1.92b**	**1.32** (10)	4	48	***40***[e]	***>98***
8		Et_2Zn		**1.93b**	**1.45** (2.4)	1	6	***90***	***96***
9		Et_2Zn		**1.93b**	**1.32** (2.4)	1	6	91	98
10		*i*-Pr_2Zn		**1.94b**	**1.32** (10)	4	12	93	84
11		*i*-Pr_2Zn		**1.94b**	**1.38** (10)	4	12	***91***	***90***
12				**1.95b**	**1.45** (2.4)	1	12	***78***	***96***
13	 **1.88**	Me_2Zn		**1.96b**	**1.45** (10	4	12	<2	--
14		Me_2Zn		**1.96b**	**1.32** (10)	4	12	***66***	***98***
15		Et_2Zn		**1.97b**	**1.45** (10)	4	6	***84***	***94***
16		Et_2Zn		**1.97b**	**1.32** (10)	4	6	75	89

[a] 3 equiv dialkylzinc, N_2 atm. [b] Yield of isolated ACA products. Aldol products were isolated as a mixture of *trans-erythro* and *trans-threo* 1:1-4:1. Oxidation proceeded in >85% [c] Determined by chiral HPLC (Chiralpak AS). [d] <2% conv observed. [e] Reaction carried out at -15 °C, 67% conv.

The limits of this method, in terms of substrate scope, were discovered when substrates **1.98**-**1.100** were examined. Sterically hindered lactone **1.98**[34] or highly conjugated systems such as **1.99** and **1.100** failed to undergo any reaction under all conditions attempted.

Scheme 1.21: Unreactive Substrates

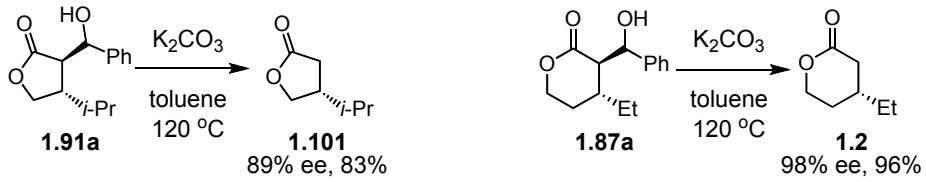


The products obtained through reactions illustrated in Table 1.2, which bear an α-substituent, were not the original products we sought to prepare through ACA to unsaturated lactones (e.g., **1.2**). Therefore, we developed a set of conditions that would efficiently unmask the β-hydroxy carbonyls (i.e., **1.87a**) to provide the products from direct ACA to unsaturated lactones (Scheme 1.22). Since an aldol reaction was used to prepare ACA adducts **1.91a** and **1.87a**, retro-aldol reaction seemed perfectly suited to cleave the requisite C-C bond and provide the direct conjugate addition adduct.[35] We were able to establish that treatment of either **1.91a** or **1.87a** with K_2CO_3 in refluxing toluene provided **1.101** and **1.2** in 83% and 96% yield, respectively.

(34) Unsaturated lactone **1.98** was prepared in accordance with reported procedures. "Palladium-Catalyzed Cyclocarbonylation of Terminal and Internal Alkynols to 2(5*H*)-Furanones," Yu, W. Y.; Alper, H. *J. Org. Chem.* **1997**, *62*, 5684-5687.

(35) The idea for retroaldol fragmentation was borrowed from related reactions involving thermal decomposition of acetone/alkyne adducts. For reference, see: "Enantioselective Addition of 2-Methyl-3-butyn-2-ol to Aldehydes: Preparation of 3-Hydroxy-1-butynes," Boyall, D.; López, H.; Sasaki, D,; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233-4236.

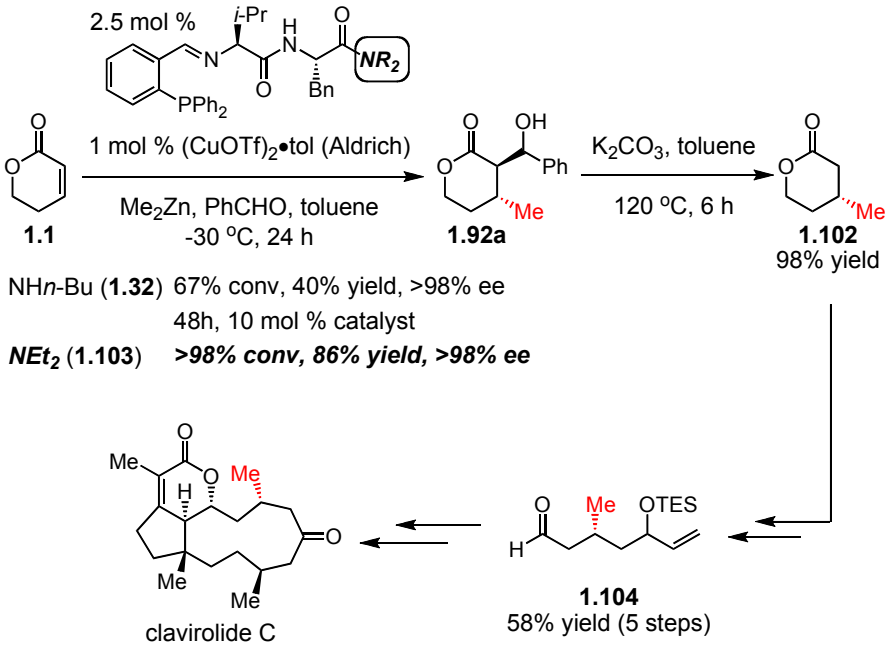
Scheme 1.22: Unmasking of ACA Products



Recently, in the context of an enantioselective total synthesis of clavirolide C,[36] synthesis of a key fragment (**1.104**) required Cu-catalyzed ACA of Me_2Zn to unsaturated lactone **1.1**; however, as reported, this particular reaction was inefficient (60% conv, 40% yield, >98% ee, 10 mol % catalyst, entry 4, Table 1.2). We were able to optimize this transformation by employing chiral ligand **1.103**, bearing an NEt_2 terminus, and **1.92a** was obtained in 86% yield (>98% conv, 24 h, 2.5 mol %) and >98% ee (Scheme 1.23).[37]

(36) (a) "Enantioselective Total Synthesis of Clavirolide C. Applications of Cu-Catalyzed Asymmetric Conjugate Additions and Ru-Catalyzed Ring-Closing Metathesis," Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, ASAP. (b) See Chapter 4.
(37) In related Cu-catalyzed ACAs, this modification was already employed; see ref (22b).

Scheme 1.23: Improvement of Reaction Efficiency by Ligand Modification

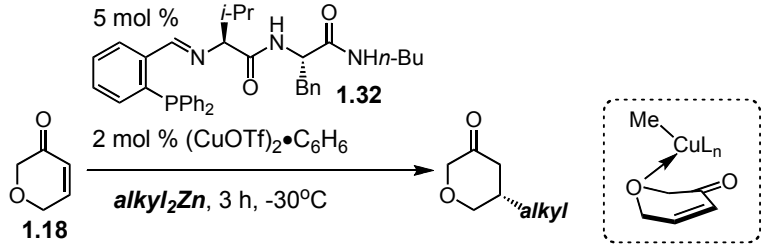


1.4.b Cu-Catalyzed ACA to 3-Oxacyclohexenones

Next, we turned our attention toward Cu-catalyzed ACA to 3-oxacyclohexenone **1.18**, an activated class of cyclic unsaturated carbonyls. ACA of Et_2Zn and Me_2Zn to unsaturated pyranone **1.18**, carried out in toluene and promoted by 5 mol % **1.32** and 2 mol % $(CuOTf)_2 \bullet C_6H_6$, resulted in only moderate selectivities (entries 1 and 4, Table 1.3). We reasoned that the neighboring Lewis basic oxygen might direct the conjugate addition by a non-selective pathway (inset, Table 1.3); performing the reaction in coordinating solvents should disfavor this chelation. Indeed, reactions carried out in ethereal solvents proved to be significantly more selective, with *THF giving rise to high enantioselectivity* (entries 3 and 5, Table 1.3). Remarkably, the rate of reaction of **1.18**

was faster in THF than in toluene, while Cu-catalyzed ACA of Et_2Zn to lactone **1.1** in THF resulted in <2 % conversion.

Table 1.3: Cu-Catalyzed ACA to Pyranone **1.18**[a]



entry	$alkyl_2Zn$	solvent	prod.	Yield (%)[b]	ee (%)[c]
1	Et_2Zn	toluene	**1.105**	n.d.	64
2	Et_2Zn	Et_2O	**1.105**	n.d.	72
3	***Et_2Zn***	***THF***	**1.105**	***66***	***98***
4	Me_2Zn	toluene	**1.106**	n.d.	56
5	***Me_2Zn***	***THF***	**1.106**	***58***	***>98***

[a] 3 equiv of $alkyl_2Zn$, N_2 atm. [b] Isolated yields [c] Determined by chiral GLC. n.d. = not determined

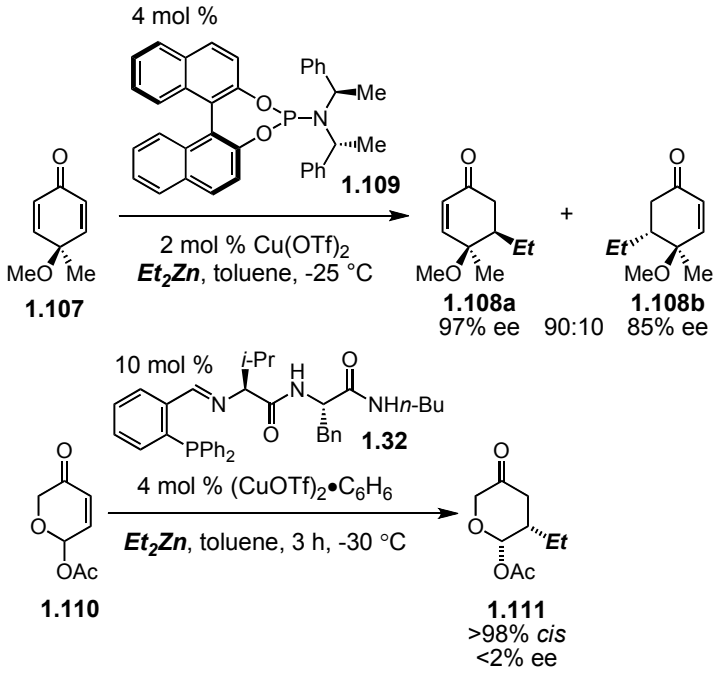
The purported O-Cu chelation has been observed in related Cu-catalyzed conjugate addition reactions. As illustrated in Scheme 1.24, Cu-catalyzed ACA to cyclohexadienone **1.107** preferentially provided the product arising from addition *cis* to the alkoxy unit **(1.108a)**.[38,39] The authors proposed that the observed diastereoselectivity was due to the neighboring alkoxy group directing the addition. While our attempts to carry out enantioselective Cu-catalyzed ACA to **1.110** led to racemic product; high

(38) (a) "Highly Enantioselective Catalytic Conjugate Additions to Cyclohexadienones," Imbos, R.; Brilman, M. H. G.; Pineschi, M,; Feringa, B. L *Org. Lett.* **1999**, *1*, 623-625. (b) "A Catalytic Enantioselective Route to *cis*- and *trans*-3,4,4,5-Tetrasubstituted Cyclohexanones; Remarkable Chiral Catalyst Control in Sequential Catalytic 1,4 Additions to Cyclohexadienones," Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2001**, *57*, 2485-2489.

(39) For a proposed O-directed Cu-promoted conjugate addition, see: "Unexpected *cis*-Selective 1,4 Addition Reaction of Lower Order Cyanocuprates to Optically Ative 5-(*tert*-Butyldimethylsiloxy)-2-cyclohexenones," Hareau-Vittini, G.; Hikichi, S.; Sato, F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2099-2101.

diastereoselectivity was observed in favor of addition *syn* to the –OAc moiety (formation of **1.111**).[40] It is likely that the diastereoselectivity observed was due to a directing effect of the neighboring acyl group.

Scheme 1.24: Directing Effects in Cu-Catalyzed ACA Reactions



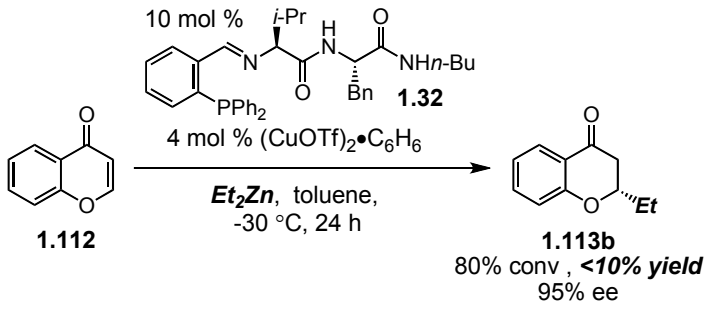
1.4.c Cu-Catalyzed ACA to Cyclic Vinylogous Esters

When more electron-rich unsaturated carbonyl **1.112** was subjected to 10 mol % **1.32**, 4 mol % $(CuOTf)_2 \bullet C_6H_6$, and Et_2Zn, similar results to the unsaturated lactones were observed; reactions delivered the ACA adducts **1.113b** in high enantioselectivity (95% ee) but in low isolated yields (80% conv, 10% yield, Scheme 1.25). Again, we reasoned that the generated zinc-enolate was likely responsible for the low yield of isolated

(40) For oxygen promoted direct addition of Et_2Zn to this class of substrates (*anti*-product favored), see: "Remarkable O_2-Effect in 1,4-Additions of Diethylzinc to 6-Acyloxy-2*H*-pyran-3(6*H*)-ones and 6-Alkoxy-2*H*-pyran-3(6*H*)-ones," van der Deen, H.; Kellogg, R. M.; Feringa, B. L. *Org. Lett.* **2000**, *2*, 1593-1595

product. In this case, β-elimination (vs. ketene formation) as well as Michael addition were the possible modes of decomposition.

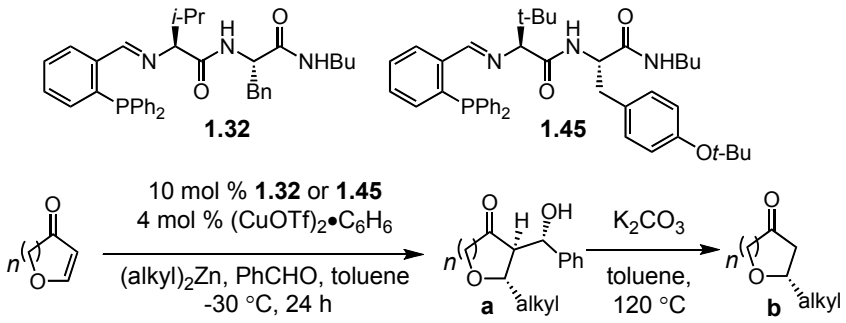
***Scheme 1.25*:** Cu-Catalyzed ACA to Chromenone **1.112**

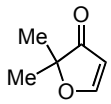
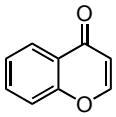


Analogous to ACA to unsaturated lactones, reactions carried out in the presence of benzaldehyde provided the enantiomerically enriched ketones in good yields (54-68%) and excellent enantioselectivities (98->98% ee, Table 1.4). Several points regarding the data in Table 1.4 merit mention: (1) not only were the ACA adducts **1.113a**, **1.115a** and **1.116a** isolated in high enantioselectivity but also in high diastereoselectivity (9:1 to >30:1).[41] This observation was in contrast to reactions involving unsaturated lactones where low diastereoselectivities were observed (1:1-4:1 dr, Table 1.2). The stereochemistry of the major diastereomer can easily be rationalized if the aldol addition proceeds through a chair-like transition state. (2) The ACA products could be converted to **1.113b**, **1.114b** and **1.115b** by retroaldol fragmentation in good yield (74-92%). (3) Cu-catalyzed ACAs involving the less reactive Me_2Zn were inefficient (entries 1 and 3, Table 1.4).

(41) The identity of the major diastereomer was confirmed by ^{1}H NMR analysis of the corresponding dimethylacetal. See the Experimentals section for details.

Table 1.4: Cu-Catalyzed ACA to Cyclic Vinylogous Esters[a]



entry	substrate	$(alkyl)_2Zn$	ligand	product	conv (%)[b]	yield (%)[c]	dr[b]	ee (%)[d]	product	yield (%)[c]
1	 **1.114**	Me_2Zn	**1.32**	--	<2	--	--	--	--	--
2		Et_2Zn	**1.32**	**1.115a**	>98	68	>30:1	>98	**1.115b**	74
3	 **1.112**	Me_2Zn	**1.32**	--	<2	--	--	--	--	--
4		Et_2Zn	**1.32**	**1.113a**	44	--	9:1	97	**1.113b**	92
5		Et_2Zn	**1.45**	**1.113a**	80	63	9:1	>98	**1.113b**	92
6		*i*-Pr_2Zn	**1.45**	**1.116a**	71	54	9:1	98	**1.116b**	84

[a] 3 equiv dialkylzinc, N_2 atm. [b] Determined by 400 MHz ^1H NMR. Mixture of *trans-erythro* and *trans-threo*. [c] Yield of isolated product. [d] Determined by chiral HPLC or GLC.

1.5 *Preparation of Air-Stable and Catalytically Active Cu-Peptide Complexes*

One of the significant aspects of the present study was the development of air-stable Cu(I)-peptide complexes **1.117**–**1.119** (Scheme 1.26).[42] We began these investigations for several reasons: (1) to gain insight to the structure of the active Cu catalyst; (2) development of efficient and selective catalytic systems that alleviate the need for glovebox techniques; and (3) synthesis of new catalysts with possibly unique reactivity.

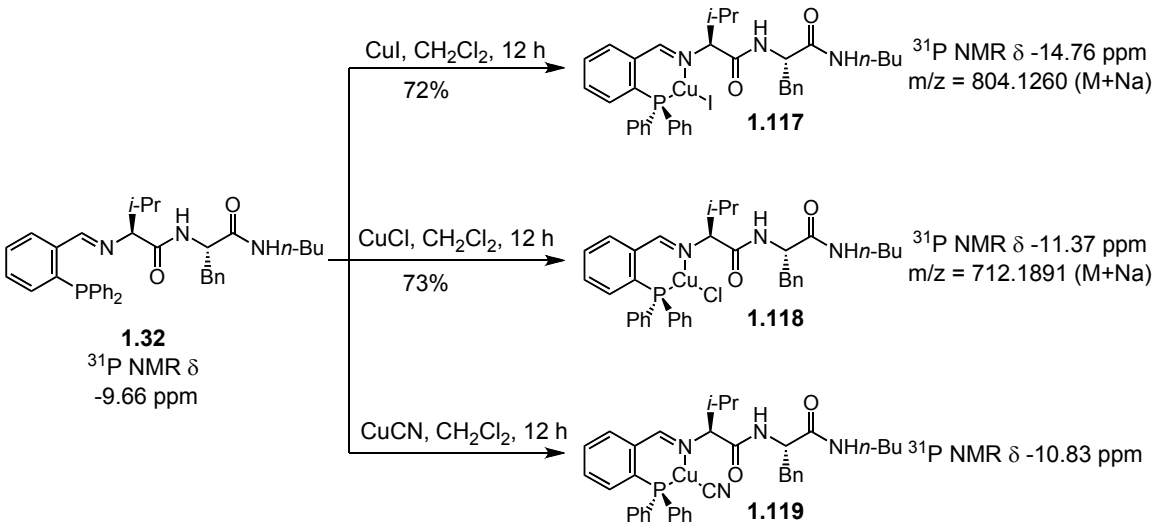
(42) Subsequent to our disclosure reference, Pfaltz and coworkers described the isolation of a related Cu(II)-triflate peptide complex; see ref (24).

Attempts at isolation of a Cu(I)-triflate complex were unsuccessful due to the high air and moisture sensitivity associated with Cu(I)OTf and, presumably, the derived Cu-peptide complexes. Therefore, we turned our attention to more air- and moisture- stable Cu salts. Initial investigations revealed that preparation of CuI, CuCl and CuCN complexes with **1.32** in toluene or benzene required several days for complete complex formation. We reasoned that slow rate of reaction in non-polar solvents was partially due to the low solubility of the Cu complexes in aromatic solvents. Thus, complex formation was carried out in more polar solvents (CH_2Cl_2, THF) and, as expected, complete conversion to the Cu-peptide complexes **1.117**-**1.119** was observed within 12 h at 22 °C. The Cu complexes were easily prepared and isolated as orange powders without the aid of glovebox techniques. These complexes have been characterized spectroscopically by ^{1}H NMR, ^{31}P NMR and HRMS.[43,44]

(43) We were unable to obtain suitable crystals for X-ray analysis. See Scheme 1.28 for an X-ray crystal structure of a related Cu-peptide complex.

(44) For a related AgOAc-amino acid based ligand complex, see: "Ag-Catalyzed Diastereo- and Enantioselective Vinylogous Mannich Reactions of α-Ketoimine Esters," Wieland, L. C.; Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc. Submitted for publication*.

Scheme 1.26: Preparation of Stable Cu-Peptide Complexes

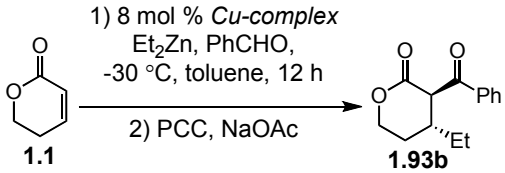


Several points regarding ACA reactions of Cu-complexes **1.117**-**1.119** are noteworthy: (1) As illustrated in Table 1.5, Cu complexes efficiently and selectively promote ACA of Et_2Zn to unsaturated lactone **1.1** when carried out on the benchtop.[45] (2) Higher catalyst loading was necessary to achieve high conversion with these complexes (vs. in situ-generated Cu-OTf complexes) presumably due to less catalyst being initiated by the dialkylzinc reagent. (3) CuCl complex **1.118** was less stable to air than CuI complex **1.117** – ACA of Et_2Zn to **1.1** with seven day old CuCl complex **1.118** stored in air resulted in 87% yield and 72% ee, while seven day old CuI complex **1.117** stored in air showed no erosion in selectivity or yield. (4) Generation of the complexes *in situ* resulted in a less selective transformation most likely due to incomplete complex

(45) For a CuI-phosphoramidite complex that is not catalytically active, see: "Enantioselective Conjugate Addition of Dialkylzinc Reagents to Cyclic and Acyclic Enones Catalyzed by Chiral Copper Complexes of New Phosphorus Amidites," de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **1996**, *35*, 2374-2430.

formation in toluene (compare entries 1 and 3 with entries 2 and 4, respectively, Table 1.5).

Table 1.5: Cu-Catalyzed ACA with Air-Stable Cu-Peptide Complexes[a]



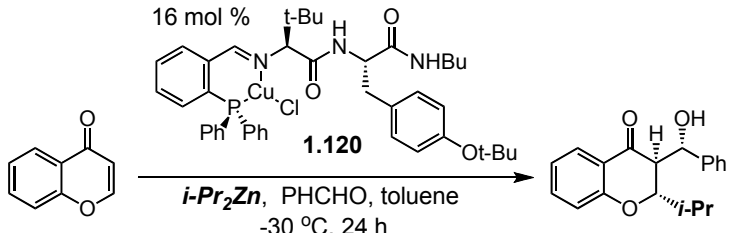
1.1 **1.93b**

entry	*Cu-Complex*	conv (%)[b]	yield (%)[c]	ee (%)[d]
1	CuI + **1.32**	57	24	63
2	**1.117**	92	74	***89***
3	CuCl + **1.32**	92	51	90
4	**1.118**	92	87	***94***

[a] 3 equiv Et_2Zn, N_2 atm. [b] Determined by 400 MHz ^1H NMR analysis. [c] Yield of isolated ACA product. Oxidation proceeded in 88% yield. [d] Determined by chiral HPLC.

Syntheses of chiral Cu-complexes were not limited to **1.32**, as illustrated in Scheme 1.27. Cu-catalyzed ACA of *i*-Pr_2Zn promoted by CuCl-complex **1.120** provided **1.116a** in 40% yield (56% conv), 95% ee, and as an 8:1 mixture of diastereomers (compare to entry 5, Table 1.4).

Scheme 1.27: Reaction with Chiral Cu-Peptide Complex **1.120**



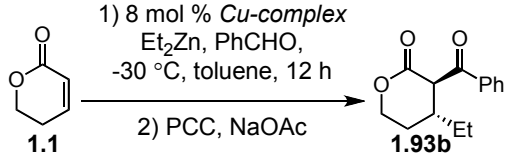
1.120

1.112

1.116a
56% conv, 40% yield
95% ee. 8:1 dr

Interestingly, air stable CuCN complex **1.119**, though less selective, afforded **1.93b** with the opposite absolute configuration than with Cu-halide complexes **1.117** and **1.118** (Table 1.6). In addition, performing the reaction in ethereal solvents (THF, Et_2O) gave rise to increased selectivity (entries 3 and 4, Table 1.6) and improved reactivity when carried out in Et_2O (entry 4, Table 1.6). One possible rational that may account for the reversal in selectivity is that CN is a non-dissociable ligand bound to Cu and therefore, addition of an dialkylzinc reagent may form an *alkyl-cuprate* intermediate.[46] This is in contrast to ACA of dialkylzinc reagents in the presence of Cu salts, bearing dissociable ligands (ligand = Cl, I, OTf), which might give rise to *alkyl-copper* intermediates.

Table 1.6: Cu-Catalyzed ACA with Air-Stable CuCN-Peptide Complex **1.119**[a]



1.1 **1.93b**

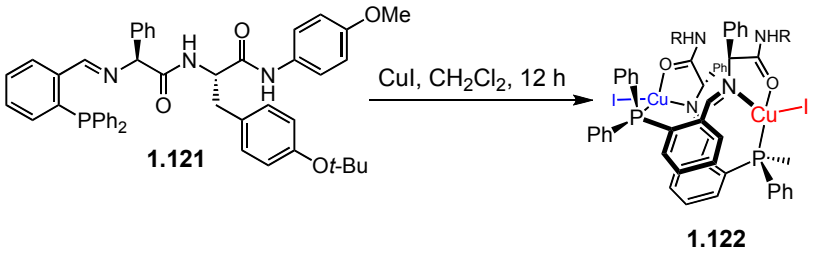
entry	*Cu-Complex*	solvent	conv (%)[b]	yield (%)[c]	ee (%)[d]
1	CuCN + **1.32**	toluene	66	22	-55
2	**1.119**	toluene	84	63	-54
3	**1.119**	THF	74	40	-79
4	**1.119**	Et_2O[e]	85	85	-70

[a] 3 equiv Et_2Zn, N_2 atm. [b] Determined by 400 MHz ^1H NMR. [c] Yield of isolated ACA product. Oxidation proceeds in 88% yield. [d] Determined by chiral HPLC analysis. [e] Reaction time: 2h

(46) "The Chemistry of Higher Order Organocuprates," Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005-5038.

In related studies, an X-ray crystal structure was obtained for a Cu-peptide complex (**1.122**).[47] As illustrated in Scheme 1.28, CuI-peptide **1.122** complex was prepared by reaction of dipeptide **1.121** and CuI in CH_2Cl_2. The crystal structure is dimeric with complexation to the Cu atoms by the phosphine, imine nitrogen and amide moieties of the ligand. For steric considerations, it is unlikely that this is the catalytically active species; however, it does shed light on potential binding modes of copper to the Lewis basic units of the ligand.

Scheme 1.28: Synthesis and X-Ray Crystal Structure of Cu-Peptide Complex **1.122**



X-Ray of **1.122**

1.6 *Conclusions*

We have developed a highly enantioselective Cu-catalyzed ACA of dialkylzinc reagents to unsaturated furanones and pyranones promoted by chiral peptide-based ligands. The products are generated efficiently (<10 mol % catalyst) and with high enantioselectivity (generally >90% ee). For reactions involving unsaturated lactones and cyclic vinylogous esters, aldol addition to an aldehyde was required to circumvent the

(47) These studies were carried out by Jerry Leu.

instability of the generated zinc enolate. ACA of dialkylzinc reagents to 3-oxycyclic enones was carried out in THF (vs. the typically used solvent toluene) to achieve high enantioselectivity (>98% ee). Studies outline above led to the development of air-stable Cu(I)-peptide complexes. The Cu-complexes could be prepared in good yield (>70%) and used for highly enantioselective (>89% ee) and efficient ACA of dialkylzinc reagents to unsaturated carbonyls.

1.7 *Experimentals*

General. Infrared (IR) spectra were recorded on a Nicolet 210 spectrophotometer, υ_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$; δ 77.0 ppm). ^{31}P NMR spectra were recorded on a Varian Unity INOVA 400 (162 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from H_3PO_4 (δ 0.00). High-resolution mass spectrometry was preformed on a Micromass LCT ESI-MS (positive mode) at the Mass Spectrometry Facility, Boston

College and by the University of Illinois Mass Spectrometry Laboratories (Urbana, Illinois). Elemental microanalysis were preformed by Robertson Microlit Laboratories (Madison, NJ). Enantiomer ratios were determined by chiral GLC analysis (Alltech Associated Chiraldex GTA column (30m x 0.25mm), Betadex 120 column (30m x 0.25mm), Alphadex (30m x 0.25mm) or chiral HPLC analysis (Chiral Technologies Chiralpak AS column (25 cm x 0.46 cm) in comparison with authentic racemic materials. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Polarimeter.

Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 ^oC) and flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry Ar by a modified Innovative Technologies purification system: toluene and benzene were purified through a copper oxide and alumina column; CH_2Cl_2 and Et_2O were purged with argon and purified by passing them through two alumina columns. THF was purified by distillation from sodium benzophenone ketal immediately prior to use. All work-up and purification procedures were carried out with reagent solvents in air. All reagent solvents were purchased from Doe and Ingalls.

Reagents and Catalysts:

Chiral ligands 1.32, 1.38 and 1.45 were prepared according to reported procedures[48]

(48) "Modular Peptide-Based Phosphine Ligands in Asymmetric Catalysis: Efficient and Enantioselective Cu-Catalyzed Conjugate Additions to Five-, Six-, and Seven-Membered Cyclic Enones," Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755-756.

Acetic Acid was purchased from Fisher and used as received.

Allylbromide was purchased from Lancaster and used as received.

Benzaldehyde was purchased from Aldrich and distilled form CaH_2 prior to use.

(*Z*)-Benzo[*b*]oxepin-2(5*H*)-one (**1.88**) was prepared according to reported procedures.[49]

Celite 545 was purchased from Aldrich and used as received.

Copper (I) chloride was purchased from Strem and used as received.

Copper (I) iodide was purchased from Strem and used as received.

Copper (I) triflate benzene complex (2:1) was prepared according to reported procedures.[50]

Chromenone was purchased from Aldrich and used without further purification.

Dibutyltinoxide was purchased from Aldrich and used as received.

Diethylzinc (neat) was purchased from Aldrich and used as received.

5,6-Dihydro-2*H*-pyran-2-one was purchased from Aldrich and used as received.

3,4-Dihydroxy-1-butene was purchased from Aldrich and used as received.

Diisopropylzinc (1M in toluene) was purchased from Aldrich and used as received.

2,2-Dimethyl-3(2*H*)-furanone was purchased from Aldrich and used as received.

Dimethylzinc (2M in toluene) was purchased from Aldrich and used as received.

2,2-Dimethoxypropane was purchased from Aldrich and used as received.

2(5*H*)-Furanone was purchased from Aldrich and used as received.

Pyridinium chlorochromate (PCC) was purchased from Acros and used as received

(49) "Ruthenium Carbene Complexes with *N,N'*-Bis(mesityl)imidazol-2-ylidene Ligands: RCM Catalysts of Extended Scope," Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H. J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204-2207.
(50) "Cationic Olefin Complexes of Copper(I). Structure and Bonding in Group Ib Metal-Olefin Complexes," Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 1889-1897.

Sodium acetate was purchased from Aldrich and used as received.

4Å MS was purchased from Aldrich and used as received.

Potassium carbonate was purchased from Aldrich and used as received.

Ruthenium catalyst (Ru-II) (Scheme S1) (Materia) was purchased from Aldrich and used as received.

Tetrapropylammonium perruthenate (TPAP) (Aldrich) was purchased from Aldrich and used as received.

4-Methylmorpholine *N*-oxide (NMO) (Aldrich), was purchased from Aldrich and used as received.

Sodium triacetoxyborohydride (Aldrich), was purchased from Aldrich and used as received.

***p*-Toluene sulfonic acid** was purchased from Aldrich and azotroped with benzene prior to use.

ν Representative experimental procedure for three-component Cu-catalyzed conjugate addition of dialkylzinc reagents to unsaturated lactones with benzaldehyde: (CAUTION: Et_2Zn IS PYROPHORIC! USE EXTREME CAUTION!) An oven-dried 13x100 mm test tube charged with **1.38** (10.1 mg, 0.0150 mmol) and $(CuOTf)_2 \bullet C_6H_6$ (3.0 mg, 0.0060 mmol), weighed out under a N_2 atmosphere in a glove box, was sealed with a septum and parafilm and removed from the glove box. Toluene (1.0 mL) was added followed by 2(5*H*)-furanone (**1.15**) (11.0 μL, 0.150 mmol) and

benzaldehyde (29.0 μL, 0.300 mmol) to provided an orange solution. The mixture was allowed to cool to –30 °C and Et_2Zn (46.0 μL, 0.450 mmol) was added. The mixture was allowed to stir at –30 °C for 6 h at which time the reaction was quenched by addition of saturated aqueous solution of NH_4Cl (1 mL) then H_2O (1 mL). The aqueous layer was washed with EtOAc (2 x 2 mL). The combined organic layers were passed through a short plug of silica gel with EtOAc and the filtrate was concentrated *in vacuo* which provided a clear oil. Purification by silica gel chromatography (30% diethyl ether/hexanes) delivered **1.38a** a clear oil (23.7 mg, 0.101 mmol, 67%).

4-Ethyl-3-hydroxy(phenyl)methyl)-dihydrofuran-2(3*H*)-one (1.90a). Analyzed as a 4:1 mixture of *trans-erythro* and *trans-threo* diastereomers, relative configuration not determined. **IR (neat):** 3461 (br m), 2969 (m), 2925 (w), 1764 (s), 1455 (m), 1394 (m), 1327 (w), 1178 (m), 1012 (s), 769 (w), 703 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37-7.26 (10H, m, major + minor), 5.36 (1H, br s, minor), 4.81 (1H, d, *J* = 8.4 Hz, major), 4.38 (1H, t, *J* = 8.4 Hz, minor), 4.28 (1H, t, *J* = 8.4 Hz, major), 4.20 (1H, br s, major), 3.82 (1H, dd, *J* = 8.8, 6.8 Hz, minor), 3.79 (1H, t, *J* = 8.8 Hz, major), 2.77 (1H, br s, minor), 2.59 (1H, dd, *J* = 3.2, 7.6 Hz, minor), 2.56-2.47 (2H, m, major + minor), 2.16 (1H, m, major), 1.16-0.97 (2H, m, minor), 0.98-0.77 (2H, m, major), 0.63 (3H, t, *J* = 7.2 Hz, major), 0.59 (3H, t, *J* = 7.6 Hz, minor); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 179.6 (major), 178.7 (minor), 141.3 (minor), 140.4 (major), 128.8 (major), 128.8 (major), 128.7 (minor), 128.0 (minor), 126.9 (major), 125.6 (minor), 74.9 (major), 72.8 (minor), 72.3 (major), 72.0 (minor), 53.2 (minor), 51.7 (major), 39.5 (major), 36.3 (minor), 26.5

(minor), 25.2 (major), 11.0 (major + minor); **HRMS (ESI+):** Calcd for $C_{13}H_{16}O_3$: 220.1099 Found: 220.1097.

3-Hydroxy(phenyl)methyl)-4-isopropyl-dihydrofuran-2(3*H*)-one (1.91a). Analyzed as a 4:1 mixture of *trans-erythro* and *trans-threo* diastereomers, relative configuration not determined. **IR (neat):** 3463 (br), 2958 (m), 2924 (w), 2872 (w), 1766 (s), 1490 (w), 1456 (w), 1393 (w), 1187 (m), 1049 (m), 992 (w), 911 (w), 768 (w), 705 (m), 676 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39-7.26 (10H, m, major + minor), 5.36 (1H, d, *J* = 2.8 Hz, minor), 4.88 (1H, d, *J* = 7.6 Hz, major), 4.27 (1H, t, *J* = 9.2 Hz, minor), 4.07-3.94 (3H, m, major + minor), 3.73 (1H, br s, major), 2.71 (1H, t, *J* = 7.2 Hz, major), 2.67 (1H, dd, *J* = 5.2, 3.2 Hz, minor), 2.39-2.33 (1H, m, minor), 2.26-2.19 (1H, m, major), 1.43-1.34 (1H, m, minor), 1.26-1.14 (1H, m major), 0.71 (3H, d, *J* = 6.8 Hz, major), 0.68 (3H, d, *J* = 6.8 Hz, major), 0.63 (3H, d, *J* = 6.8 Hz, minor), 0.56 (3H, d, *J* = 6.8 Hz, minor); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 179.2 (major), 179.1 (minor), 141.2 (minor), 140.3 (major), 128.8 (major), 128.7 (minor), 128.7 (major), 128.0 (minor) 126.7 (major), 125.7 (minor), 74.6 (major), 73.3 (minor), 70.9 (minor), 69.1 (major), 50.7 (minor), 49.5 (major), 43.1 (major), 40.5 (minor), 30.2 (minor), 28.6 (major), 19.9 (major), 19.1 (minor), 18.2 (minor), 17.1 (major); **HRMS (ESI+):** Calcd for $C_{14}H_{18}O_3$: 234.1256 Found: 234.1258.

3-(Hydroxy(phenyl)methyl)-4-methyl-tetrahydropyran-2-one (1.92a). Analyzed as a 1:1 mixture of *trans-erythro* and *trans-threo* diastereomers. **IR (neat):** 3427 (br s), 3072

(w), 3034 (w), 2957 (m), 2924 (m), 2875 (w), 2859 (w), 1717 (s), 1466 (m), 1400 (m), 1269 (m), 1231 (m), 1203 (m), 1089 (m), 1061 (m), 914 (w), 876 (w), 761 (w), 706 (s), 657 (w) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39-7.26 (10H, m), 5.25 (1H, dd, *J* = 3.6, 6.8 Hz), 4.94 (1H, t, *J* = 5.2 Hz), 4.31-4.25 (2H, m), 4.18-4.13 (1H, m), 4.04 (1H, td, *J* = 10.4, 2.0 Hz), 3.92 (1H, d, *J* = 4.8 Hz), 3.83 (1H, d, *J* = 6.4 Hz), 2.65 (1H, dd, *J* = 8.4, 3.6 Hz), 2.52 (1H, t, *J* = 6.4 Hz), 2.04-1.88 (3H, m), 1.83-1.76 (1H, m), 1.58-1.47 (2H, m), 0.82 (3H, d, *J* = 6.8 Hz), 0.76 (3H, d, *J* = 6.8 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 174.4, 174.1, 141.4, 141.3, 128.7, 128.6, 128.2, 128.1, 126.8, 126.5, 74.4, 73.7, 68.2, 66.8, 55.2, 54.6, 31.6, 31.1, 27.9, 27.2, 21.5, 21.3; **HRMS (ESI+):** Anal. Calcd for $C_{13}H_{16}O_3$: 220.1099 Found: 220.1099.

4-Ethyl-3-(hydroxy(phenyl)methyl)-tetrahydropyran-2-one (1.93a). Analyzed as a 1.6:1 mixture of *trans-erythro* and *trans-threo* diastereomers, relative configuration not determined. **IR (neat):** 3427 (br, s), 3056 (w), 3024 (w), 2968 (s), 2905 (m), 2855 (m), 1703 (s), 1451 (m), 1432 (m), 1269 (s), 1237 (m), 1086 (m), 1061 (m), 765 (w), 702 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39-7.27 (10H, major + minor), 5.24 (1H, dd, *J* = 6.8, 3.6 Hz, major), 4.93 (1H, dd, *J* = 6.0, 4.8 Hz, minor), 4.30-4.24 (2H, m, major + minor), 4.16 (1H, ddd, *J* = 11.2, 6.4, 4.0 Hz, minor), 3.99 (1H, ddd, *J* = 11.2, 10.0, 2.4 Hz, major), 3.80 (1H, d, *J* = 4.8 Hz, minor), 3.71 (1H, d, *J* = 6.8 Hz, major), 2.71 (1H, dd, *J* = 7.2, 3.6 Hz, major), 2.61 (1H, t, *J* = 6.4 Hz, minor), 1.95-1.75 (4H, m, major + minor), 1.61-1.40 (2H, m, minor), 1.27-1.15 (2H, m, minor), 1.14-1.03 (2H, m, major), 0.75 (3H, t, *J* = 7.2 Hz, minor), 0.74 (3H, t, *J* = 7.2 Hz, major); **^{13}C NMR (100 MHz,**

$CDCl_3$): δ 174.0 (major), 174.0 (minor), 141.2 (major), 141.1 (minor), 128.5 (major), 128.4 (major), 128.0 (minor), 127.9 (minor), 126.6 (minor), 126.3 (major), 74.3 (minor), 74.1 (major), 67.9 (major), 66.7 (minor), 53.3 (major), 52.8 (minor), 34.1 (minor), 33.3 (major), 27.7 (major), 27.7 (major), 27.4 (minor), 27.1 (minor), 11.0 (minor), 10.8 (major); **HRMS (ESI+):** Anal. Calcd for $C_{14}H_{18}O_3Na$ ($M+Na^+$): 257.1154 Found: 257.1152.

3-(Hydroxy(phenyl)methyl)-4-(4-methylpentyl)-tetrahydropyran-2-one (1.95a). Analyzed as a 1:1 mixture of *trans-erythro* and *trans-threo* diastereomers, relative configuration not determined. **IR (neat):** 3427 (br, m), 3056 (w), 3031 (w), 2962 (s), 2911 (s), 2861 (m), 1703 (s), 1470 (s), 1406 (s), 1269 (s), 1231 (m), 1212 (m), 1092 (m), 1055 (m), 765 (w), 708 (s), 664 (m), 564 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37-7.24 (10H, m), 5.25 (1H, dd, *J* = 6.0, 3.6 Hz). 4.90 (1H, dd, *J* = 6.0, 4.0 Hz), 4.26-4.21 (2H, m), 4.14-4.08 (1H, m), 4.03 (1H, t, *J* = 9.6 Hz), 3.95-3.94 (1H, m), 3.80-3.77 (1H, m), 2.64 (1H, t, *J* = 3.2 Hz), 2.57 (1H, t, *J* = 6.4 Hz), 1.95-1.72 (4H, m), 1.54-1.29 (5H, m), 1.20-1.04 (4H, m), 1.02-0.82 (7H, m), 0.78-0.75 (12H m); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 174.1, 174.0, 141.2, 141.1, 128.3, 128.3, 127.9, 127.7, 126.6, 126.1, 74.3, 74.0, 67.8, 66.7, 53.7, 53.1, 38.5, 38.5, 35.4, 35.0, 32.4, 31.3, 28.2, 27.6, 27.6, 27.5, 24.2, 24.0, 22.5, 22.5, 22.3, 22.3; **HRMS (ESI+):** Anal. Calcd for $C_{18}H_{26}O_3Na$ ($M+Na^+$): 313.1780 Found: 313.1788.

3-(Hydroxy(phenyl)methyl)-4-isopropyl-tetrahydropyran-2-one (1.94a). Analyzed as a 1:1 mixture of *trans-erythro* and *trans-threo* diastereomers, relative configuration not determined. **IR (neat):** 3423 (br s), 2964 (s), 2924 (m), 2872 (w), 1714 (s), 1468 (w), 1410 (w), 1273 (s), 1209 (m), 1078 (m), 1055 (m), 774 (m), 705 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39-7.26 (10H, m), 5.15 (1H, br s), 4.95 (1H, d, *J* = 5.6 Hz), 4.27-4.21 (2H, m), 4.18-4.13 (1H, m), 3.91 (1H, br s), 3.86 (1H, dt, *J* = 2.4, 11.2 Hz), 3.46 (1H, br s), 2.89-2.82 (2H, m), 1.91-1.76 (3H, m), 1.73-1.48 (4H, m), 1.34-1.27 (1H, m), 0.82 (3H, d, *J* = 6.8 Hz), 0.81 (3H, d, *J* = 6.8 Hz), 0.79 (3H, d, *J* = 6.8 Hz), 0.77 (3H, d, *J* = 6.8 Hz); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 174.4, 173.7, 141.6, 141.2, 128.6, 128.5, 128.1, 128.1, 126.6, 126.5, 74.8, 74.6, 68.2, 67.4, 51.8, 51.4, 38.7, 37.9, 30.1, 30.0, 23.4, 23.2, 20.7, 20.7, 16.9, 16.8; **HRMS (ESI+):** Calcd for $C_{15}H_{20}O_3$: 248.1412 Found: 248.1418.

5-(Hydroxy(phenyl)methyl)-4-methyl-4,5-dihydrobenzo[*b*]oxepin-2(3*H*)-one (1.96a). Major diastereomer, relative configuration not determined. **IR (neat):** 3512 (bs s), 3070 (w), 3030 (w), 2973 (w), 2928 (w), 1747 (s), 1617 (w), 1577 (w), 1492 (m), 1458 (m), 1362 (m), 1237 (m), 1140 (s), 1118 (s), 998 (w), 703 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32-7.15 (8H, m), 7.00 (1H, d, *J* = 7.6 Hz), 4.78 (1H, dd, *J* = 10.8, 2.8, Hz), 4.32 (1H, d, *J* = 10.8 Hz), 3.17 (1H, dd, *J* = 14.0, 6.4 Hz), 3.01-2.92 (1H, m), 2.48 (1H, dd, *J* = 10.0, 3.2 Hz), 2.43 (1H, dd, *J* = 14.0, 1.2 Hz), 1.01 (3H, d, *J* = 6.9 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 173.8, 150.6, 142.5, 131.1, 128.8, 128.5, 127.8, 127.5, 125.8, 125.6, 119.1, 71.6, 54.1, 36.2, 35.9, 17.9; **HRMS (ESI+):** Calcd for $C_{18}H_{18}O_3$: 282.1255 Found: 282.1263.

4-Ethyl-5-(hydroxy(phenyl)methyl)-4,5-dihydrobenzo[*b*]oxepin-2(3*H*)-one (1.97a). Major diastereomer, relative configuration not determined. **IR (neat):** 3511 (bs s), 3061 (w), 3028 (w), 2973 (w), 2923 (w), 2867 (w), 1750 (s), 1489 (m), 1456 (m), 1362 (w), 1223 (s), 1134 (s), 1112 (s), 1000 (w), 700 (w), 673 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.31-7.10 (8H, m), 7.00 (1H, d, *J* = 7.6 Hz), 4.78 (1H, d, *J* = 8.0 Hz), 4.34 (1H, d, *J* = 10.8 Hz), 2.96 (1H, dd, *J* = 14.4, 6.4 Hz), 2.73 (1H, dd, *J* = 14.4, 2.0 Hz), 2.68-2.61 (1H, m), 2.56 (1H, dd, *J* = 10.0, 3.2 Hz), 1.56-1.48 (1H, m), 1.21-1.10 (1H, m), 1.02 (3H, t, *J* = 7.2 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 173.8, 150.7, 142.7, 130.9, 128.8, 128.6, 128.2, 127.5, 125.9, 125.7, 119.1, 71.4, 53.7, 42.7, 31.4, 23.5, 11.9; **HRMS (ESI+):** Calcd for $C_{19}H_{20}O_3$: 296.1412 Found: 296.1409.

ν Representative experimental procedure for oxidation with PCC: Alcohol **1.90a** (24.0 mg, 0.109 mmol) dissolved in undistilled CH_2Cl_2 (4 mL), was added to a 10 mL round bottom flask charged with PCC (45.6 mg, 0.212 mmol), NaOAc (17.3 mg, 0.212 mmol), oven dried powdered 4 Å MS (10 mg) and Celite® (~18 mg). The mixture was allowed to stir for 3 h, at which time Et_2O (~6 mL) was added, and the mixture was passed through a short plug of Celite® layered on top of silica gel eluted with Et_2O. Removal of solvent *in vacuo* and exposure to high vacuum (~2.0 mmHg) for 1 h, to remove trace quantities of acetic acid, provided pure **1.90b** as a clear oil (22.7 mg, 0.104 mmol, 98%).

3-Benzoyl-4-ethyl-dihydrofuran-2(3*H*)-one (1.90b). IR (neat): 2967 (w), 2923 (w), 2879 (w), 1778 (s), 1677 (s), 1602 (m), 1457 (m), 1274 (m), 1230 (m), 1155 (s), 1016(m), 859 (w), 777 (w), 689 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.04 (2H, dd, *J* = 8.4, 0.8 Hz), 7.61 (1H, tt, *J* = 6.8, 0.8 Hz), 7.52-7.47 (2H, m), 4.58 (1H, dd, *J* = 8.8, 7.6 Hz), 4.24 (1H, d, *J* = 6.8 Hz), 4.04 (1H, dd, *J* = 8.8, 6.4 Hz), 3.16-3.07 (1H, m), 1.62-1.54 (2H, m), 0.92 (3H, t, *J* = 7.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 193.4, 172.9, 135.9, 134.2, 129.6, 129.0, 72.4, 54.5, 41.0, 25.9, 11.8; **Anal. Calcd. for $C_{13}H_{14}O_3$:** C, 71.54; H, 6.47; Found: C, 71.38; H, 6.79; **Optical Rotation:** $[\alpha]_D^{20}$ –124 (*c* 0.853, $CHCl_3$) for an enantiomerically enriched sample of 97% ee.

The enantiomeric purity of the conjugate addition product product was established by chiral HPLC analysis (Chiralpak AS column, 78:22 hexanes/*i*PrOH, t_{minor} = 10.9 min, t_{major} = 16.5 min).

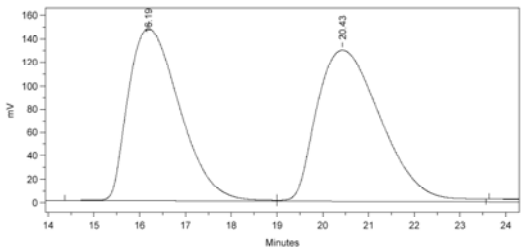
3*R*,4*S*)-3-Benzoyl-4-isopropyl-dihydrofuran-2(3*H*)-one (1.91b). IR (neat): 2961 (m), 2925 (w), 2889 (w), 1762 (s), 1690 (s), 1606 (w), 1576 (w), 1444 (w), 1228 (w), 1168 (s), 1024 (m), 688 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.04 (2H, d, *J* = 8.4 Hz), 7.61 (1H, t, *J* = 6.8 Hz), 7.50 (2H, t, *J* = 6.8 Hz), 4.56 (1H, dd, *J* = 8.0, 8.0 Hz), 4.33 (1H, d, *J* = 8.0 Hz), 4.09 (1H, dd, *J* = 8.0, 8.0 Hz), 3.09 (1H, q, *J* = 8.0 Hz), 1.78-1.70 (1H, m), 0.93 (3H, d, *J* = 6.8 Hz), 0.84 (3H, d, *J* = 6.8 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 193.6, 173.1, 136.0, 134.1, 129.5, 128.9, 71.1, 52.7, 45.8, 31.6, 20.9, 19.8; **Anal. Calcd**

for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; Found: C, 72.06; H, 7.08; **Optical Rotation:** $[\alpha]_D^{20}$ – 87.3 (*c* 1.35, $CHCl_3$) for an enantiomerically enriched sample of 89% *ee*.

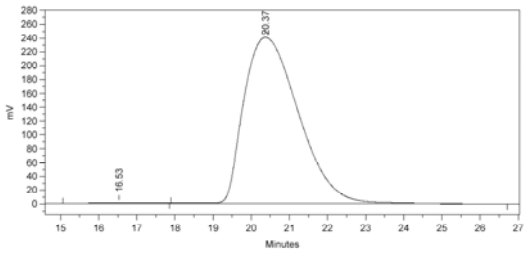
The enantiomeric purity of the conjugate addition product was established by chiral HPLC analysis (Chiralpak AS column, 80:20 hexanes/*i*PrOH, t_{minor} = 8.7 min, t_{major} = 14.5 min).

3-Benzoyl-4-methyl-tetrahydropyran-2-one (1.92b). IR (neat): 2961 (m), 2923 (m), 1740 (s), 1721 (s), 1696 (s), 1558 (m), 1262 (m), 1199 (m), 695 (m), 670 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.99-7.96 (2H, m), 7.58 (1H, tt, *J* = 6.4, 1.2 Hz), 7.50-7.46 (2H, m), 4.48-4.44 (2H, m), 4.15 (1H, d, *J* = 9.2 Hz), 2.71-2.63 (1H, m), 2.09-2.02 (1H, m), 1.75-1.65 (1H, m), 1.03 (3H, d, *J* = 6.8 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 196.2, 168.3, 137.0, 133.9, 129.2, 128.9, 68.9, 56.7, 30.5, 30.2, 20.8; **HRMS (ESI+):** Calcd for $C_{13}H_{14}O_3Na$ ($M+Na^+$): 241.0845 Found: 241.0841; **Optical Rotation:** $[\alpha]_D^{20}$ –76.7 (c 0.226, $CHCl_3$) for an enantiomerically enriched sample of >98% *ee*.

The enantiomeric purity of the conjugate addition product was established by chiral HPLC analysis (Chiralpak AS column, 78:22 hexanes:*i*PrOH). Chromatograms are illustrated below:



#	Time	Area	Height	Width	Area (%)
1	16.193	1147680	147274	1.299	48.399
2	20.433	1288430	129301	1.663	51.661



#	Time	Area	Height	Width	Area (%)
1	16.532	3712	52	1.195	0.156
2	20.373	2382936	24059	1.651	99.844

(3*R*,4*R*)-3-Benzoyl-4-ethyl-tetrahydropyran-2-one (1.93b). IR (neat): 3427 (br, w), 3075 (m), 2962 (s), 2930 (s), 2880 (s), 1734 (s), 1678 (s), 1596 (m), 1451 (m), 1413 (m), 1294 (m), 1262 (w), 1199 (w), 1073 (w), 998 (m), 935 (m), 778 (m), 696 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.02-7.88 (2H, m), 7.59 (1H, tt, *J* = 7.6, 2.0 Hz), 7.51-7.47 (2H, m), 4.48-4.45 (2H, m), 4.28, (1H, d, *J* = 8.4 Hz), 2.58-2.49 (1H, m), 2.17-2.10 (1H, m), 1.72-1.62 (1H, m), 1.49-1.41 (1H, m), 1.40-1.29 (1H, m), 0.89 (3H, t, *J* = 7.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 196.1, 168.3, 136.6, 133.7, 129.1, 128.8, 68.5, 55.0, 36.5, 28.0, 27.1, 11.1; **HRMS (ESI+):** Calcd for $C_{14}H_{16}O_3Na$ ($M+Na^+$): 255.0994, Found: 255.0997; **Optical Rotation:** $[\alpha]_D^{20}$ –58.8 (*c* 1.05, $CHCl_3$) for an enantiomerically enriched sample of 93% *ee*.

The enantiomeric purity of the conjugate addition product was established by chiral HPLC analysis (Chiralpak AS column, 95:5 hexanes:*i*PrOH, t_{minor} = 52.6 min, t_{major} = 75.0 min).

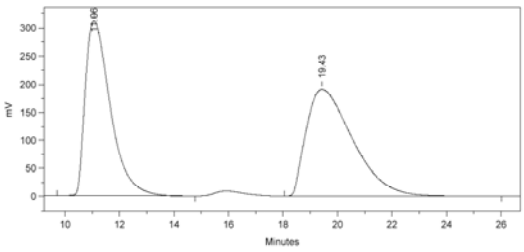
3-Benzoyl-4-(4-methylpentyl)-tetrahydropyran-2-one (1.95b). IR (neat): 3522 (br, w) 3062 (w), 2955 (s), 2917 (s), 2867 (s), 1734 (s), 1678 (s), 1596 (w), 1476 (m), 1445 (s), 1413 (m), 1269 (m), 1193 (w), 1070 (m), 998 (m), 948 (m), 771 (s), 696 (s), 595 (w), 513 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.05-7.98 (2H, m), 7.58 (1H, tt, *J* = 7.6, 1.2 Hz), 7.50-7.46 (2H, m), 4.47-4.43 (2H, m), 4.26 (1H, d, *J* = 8.4 Hz), 2.64-2.54 (1H, m), 2.16-2.09 (1H, m), 1.71-1.61 (1H, m), 1.47-1.37 (1H, m), 1.36-1.15 (4H, m), 1.10-1.04 (2H, m), 0.78 (3H, t, *J* = 3.2 Hz), 0.77 (3H, t, *J* = 3.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 196.2, 186.2, 136.6, 133.7, 129.0, 128.7, 68.5, 55.3, 38.6, 35.5, 35.0, 27.7, 27.6, 24.3, 22.5, 22.3; **Anal. Calcd for $C_{18}H_{24}O_3$:** C, 74.97; H, 8.39; Found: C, 74.96; H, 8.16; **Optical Rotation:** $[\alpha]_D^{20}$ –56.6 (*c* 1.02, $CHCl_3$) for an enantiomerically enriched sample of 94% *ee*.

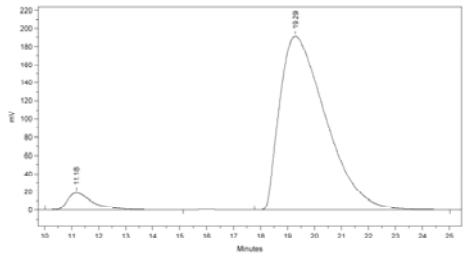
The enantiomeric purity of the conjugate addition product was established by chiral HPLC analysis (Chiralpak AS column, 95:5 hexanes:*i*PrOH, t_{minor} = 38.4 min, t_{major} = 48.1 min).

(3-Benzoyl-4-isopropyl-tetrahydropyran-2-one (1.94b). IR (neat): 2967 (m), 2919 (w), 2883 (w), 1744 (s), 1678 (s), 1606 (w), 1450 (m), 1294 (m), 1276 (m), 1198 (s), 1150 (m), 1078 (m), 946 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.02 (2H, dd, *J* = 8.4, 0.8 Hz), 7.58 (1H, tt, *J* = 7.2, 0.8 Hz), 7.49-7.45 (2H, m), 4.47-4.38 (3H, m), 2.56 (1H, dddd, *J* = 13.6, 10.4, 8.4, 5.6 Hz), 1.99 (1H, dddd, *J* = 13.6, 7.6, 6.0, 3.6 Hz), 1.77-1.67 (1H, m), 1.67-1.55 (1H, m), 0.86 (6H, d, *J* = 6.8 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 196.5, 168.8, 136.6, 133.9, 129.4, 129.0, 68.8, 53.3, 41.0, 31.2, 24.4, 20.5, 18.1; **Anal.**

Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; Found: C, 72.96; H, 7.47; **Optical Rotation:** $[\alpha]_D^{20}$ –45.5 (*c* 1.23, $CHCl_3$) for an enantiomerically enriched sample of 90% *ee*.

The enantiomeric purity of the conjugate addition product was established by chiral HPLC analysis (Chiralpak AS column, 80:20 hexanes:*i*PrOH). Chromatograms are illustrated below:





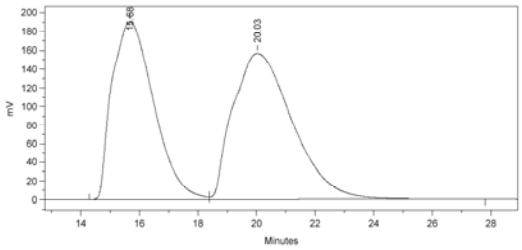
#	Time	Area	Height	Width	Area (%)
1	11.064	199351	31224	1.062	46.738
2	19.433	227179	19234	1.972	53.262

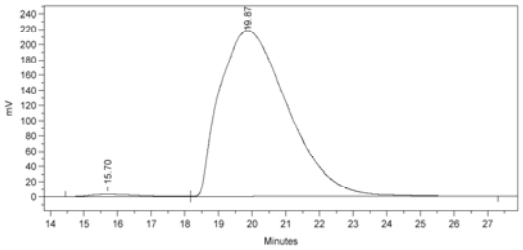
#	Time	Area	Height	Width	Area (%)
1	11.178	116144	1823	1.062	4.899
2	19.294	2254406	19049	1.972	95.101

3-Benzoyl-4-methyl-4,5-dihydro-3*H*-benzo[*b*]oxepin-2-one (1.96b). IR (neat): 2961 (w), 2963 (w), 1759 (s), 1696 (w), 1482 (w), 1451 (w), 1130 (m), 1111 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.73-7.70 (2H, m), 7.52 (1H, dt, *J* = 7.3, 1.3 Hz), 7.43-7.38 (2H, m), 7.36-7.32 (1H, m), 7.24-7.20 (2H, m), 7.17 (1H, d, *J* = 2.5 Hz), 3.92 (1H, d, *J* = 9.3 Hz), 3.39-3.32 (1H, m), 3.21 (1H, dd, *J* = 13.9, 6.7 Hz) 2.46 (1H, dd, *J* = 13.9, 2.2 Hz), 0.96 (3H, d, *J* = 6.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 192.1, 168.7, 151.1, 136.3, 133.8, 131.3, 129.0, 129.0, 128.6, 128.3, 126.4, 119.4, 56.2, 35.5, 35.3, 19.1; **HRMS (ESI+):** Calcd for $C_{18}H_{16}O_3Na$ ($M+Na^+$): 303.0997, Found; 303.0989; **Optical**

Rotation: $[\alpha]_D^{20}$ +31.2 (*c* 1.18, $CHCl_3$) for an enantiomerically enriched sample of 96 % *ee*.

The enantiomeric purity of the conjugate addition product was established by chiral HPLC analysis (Chiralpak AS column, 98:2 hexanes:*i*PrOH) Chromatograms are illustrated below:





#	Time	Area	Height	Width	Area (%)
1	15.681	187988	19033	1.646	46.020
2	20.027	220505	15660	2.347	53.980

#	Time	Area	Height	Width	Area (%)
1	15.705	2803	2950	1.584	0.905
2	19.866	307115	218054	2.347	99.095

3-Benzoyl-4-ethyl-4,5-dihydro-3*H*-benzo[*b*]oxepin-2-one (1.97b). IR (neat): 2962 (w), 2923 (w), 1753 (s), 1696 (s), 1482 (m), 1451 (m), 1218 (m), 1130 (m), 1111 (m), 758 (w), 689 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.73-7.71 (2H, m), 7.52 (1H, dt, *J* = 7.5, 1.3 Hz), 7.42-7.38 (2H, m), 7.33-7.28 (1H, m), 7.21-7.19 (2H, m), 7.11 (1H, d, *J* = 7.9 Hz), 3.99 (1H, d, *J* = 8.6 Hz), 3.15-3.05 (1H, m), 3.04 (1H, dd, *J* = 13.9, 6.4 Hz), 2.69 (1H, dd, *J* = 13.9, 2.7 Hz), 1.31-1.15 (2H, m), 0.98 (3H, t, *J* = 7.3 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 192.2, 168.7, 150.9, 136.4, 133.7, 131.1, 129.0, 129.0, 128.8, 128.2, 126.3, 119.4, 55.8, 42.2, 31.2, 25.5, 12.1; **HRMS (ESI+):** Calcd for $C_{19}H_{18}O_3Na$

(M+Na^+): 317.1154, Found: 317.1160; **Optical Rotation:** $[\alpha]_D^{20}$ +12.5 (*c* 1.49, $CHCl_3$) for an enantiomerically enriched sample of 93% *ee*.

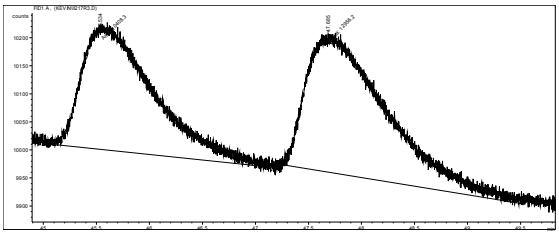
The enantiomeric purity of the conjugate addition product was established by chiral HPLC analysis (Chiralpak AS column, 98.5:1.5 hexanes:*i*PrOH, t_{minor} = 16.3 min, t_{major} = 19.0 min).

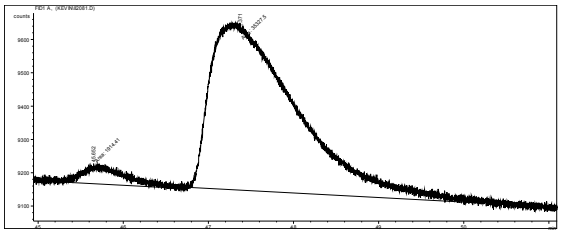
ν Representative experimental procedure for retroaldol fragmentation with K_2CO_3: The conjugate addition adduct **1.93b** (23.6 mg, 0.100 mmol) dissolved in undistilled toluene (2.0 mL) was added to a 10 mL round bottom flask charged with K_2CO_3 (15.3 mg, 0.110 mmol) and equipped with a reflux condenser. The mixture was allowed to stir at 120 °C for 1 h at which time it was allowed to cooled to 22 °C and passed through a short plug of silica gel (4 x 1 cm) eluting with Et_2O. The filtrate was then concentrated *in vacuo*. Purification by silica gel chromatography (25% diethyl ether/hexanes) provided **1.2** as a clear oil (12.3 mg, 0.0960 mmol, 96%)

(*R*)-4-Isopropyl-dihydrofuran-2(3*H*)-one (1.101). IR (neat): 2974 (m), 2930 (s), 2854 (w), 1784 (s), 1476 (w), 1180 (m), 1029 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.39 (1H, dd, *J* = 8.8, 7.6 Hz), 3.94 (1H, dd, *J* = 8.8, 8.8 Hz), 2.55 (1H, dd, *J* = 16.8, 8.0 Hz), 2.33-2.17 (2H, m), 1.67-1.55 (1H, m), 0.94 (3H, d, *J* = 6.8 Hz), 0.89 (3H, d, *J* = 6.8 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 177.5, 72.2, 42.9, 33.1, 31.9, 20.8, 20.1; **Anal. Calcd**

for $C_7H_{12}O_2$: C, 65.60; H, 9.44; Found: C, 65.37; H, 9.49; **Optical Rotation:** $[\alpha]_D^{20}$ +10.3 (c 0.240, $CHCl_3$) for an enantiomerically enriched sample of 89% ee. **Proof of Absolute Stereochemistry:** literature:[51] $[\alpha]_D$ –11 (*c* 0.52, $CHCl_3$) for 96% *ee* in the *S* enantiomer.

The enantiomeric purity of the conjugate addition product was established by chiral GLC analysis (Chiraldex GTA column, 15 psi, 100 °C). Chromatograms are illustrated below:





#	Time	Area	Height	Width	Area (%)
1	45.541	10134.6	220.8	0.7651	46.687
2	47.685	12956.2	248.1	0.8705	53.313

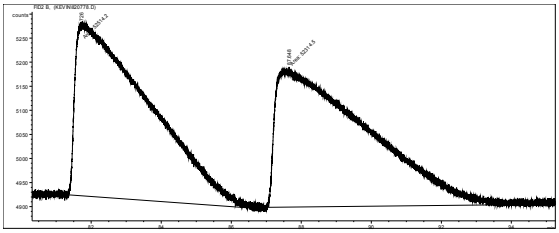
#	Time	Area	Height	Width	Area (%)
1	45.652	1914.4	60.1	0.5305	5.400
2	47.371	35327.5	502.8	1.1711	94.599

(*R*)-4-Ethyl-tetrahydropyran-2-one (1.2). IR (neat): 2962 (m), 2924 (m), 2874 (w), 1737 (s), 1462 (w), 1412 (w), 1262 (m), 1231 (m), 1175 (w), 1106 (m), 1081 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.41-4.36 (1H, m), 4.26-4.19 (1H, m), 2.67 (1H, ddd, *J* = 17.6, 6.0, 1.6 Hz), 2.12 (1H, dd, *J* = 17.6, 10.4 Hz), 1.97-1.81 (2H, m), 1.54-1.44 (1H, m), 1.37 (2H, dddd, *J* = 14.4, 7.2, 7.2, 7.2 Hz), 0.92 (3H, t, *J* = 7.6 Hz); **^{13}C NMR (100**

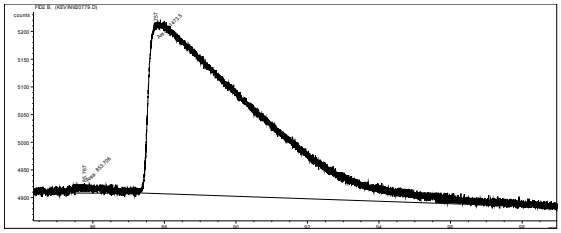
(51) "Enantioselective Synthesis of Dihydropyrans. Catalysis of Hetero Diels-Alder Reactions by Bis(oxazoline) Copper(II) Complexes," Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635-1649.

MHz, $CDCl_3$): δ 171.7, 68.7, 36.5, 33.3, 29.1, 28.7, 11.1; HRMS Calcd for $C_7H_{12}O_2Na$ ($M+Na^+$): 151.0735, Found: 151.0733; **Optical Rotation:** $[\alpha]_D^{20}$ +22 (*c* 0.51, $CHCl_3$) for an enantiomerically enriched sample of 98% *ee*. **Proof of Stereochemistry:** literature:[52] (-) value was assigned to the *S* enantiomer, but the exact value was not provided.

The enantiomeric purity of the conjugate addition product was established by chiral GLC analysis (β-Dex column, 15 psi, 110 °C). Chromatograms are illustrated below:



#	Time	Area	Height	Width	Area (%)
1	81.726	52514.2	362	2.4178	50.220
2	87.648	52314.5	292	2.9862	49.779



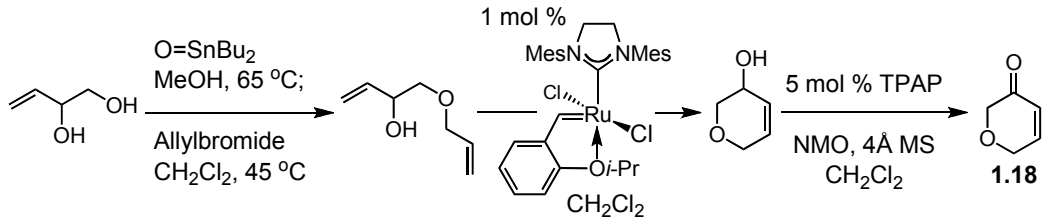
#	Time	Area	Height	Width	Area (%)
1	85.767	853.7	18.2	0.78	1.441
2	87.757	61473.5	310.4	3.3005	98.558

ν Experimental Procedures for the Preparation of 2*H*-pyran-3(6*H*)-one (1.18):[53,54]

(52) "Copper-Catalyzed Enantioselective Conjugate Addition of Grignard Reagents to Cyclic Enones," Feringa, B. L.; Badorrey, R.; Peña, D.; Harutyunyan, S. R.; Minnaard, A. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5834-5838.

(53) "Synthesis of 3-Oxooxa- and 3-Oxoazacycloalk-4-enes by Ring-Closing Metathesis. Application to the Synthesis of an Inhibitor of Cathepsin K," Taillier, C.; Hameury, T.; Bellosta, V.; Cossy, J. *Tetrahedron* **2007**, *63*, 4472-4490.

(54) A similar protocol was reported to the allylic alcohol intermediate, however experimental procedures were not provided, see: "Effect of a Proximal Oxygen Substituent on the Efficacy of Ruthenium-Catalyzed Cross-Metathesis and RCM," Maishal, T. K.; Sinha-Mahapatra, D. K.; Paranjape, K.; Sarkar, A. *Tetrahedron Lett.* **2002**, *43*, 2263-2267.



A 250 mL RBF equipped with a reflux condenser was charged with dibutyltinoxide (3.22 g, 13.0 mmol). Reagent grade MeOH (100 mL) followed by 3,4-dihydroxy-1-butene (1.09 mL, 13.0 mmol) were added and the heterogeneous mixture allowed to reflux for 1 h (mixture becomes homogeneous). The volatiles were removed under reduced pressure and CH_2Cl_2 (100 mL) followed by allyl bromide (1.18 mL, 14.0 mmol) were added. The solution was allowed to reflux for 72 h at which time silica gel was added. The volatiles were removed *in vacuo* and the resulting solid was purified by silica gel chromatography (30% ether/pentane) to yield the diene as a pale yellow oil (0.62 g, 4.84 mmol, 37%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.93-5.77 (2H, m), 5.35-5.15 (4H, m), 4.34-4.26 (1H, m), 4.01 (2H, d, J = 5.6 Hz), 3.50-3.47 (1H, m), 3.33-3.29 (1H, m), 2.54 (1H, d, J = 2.8 Hz).

To a 250 mL round bottom flask charged with Ru-catalyst **Ru-II** (15.2 mg, 0.024 mmol), was added CH_2Cl_2 (100 mL). To this green solution, the diene (312.0 mg, 2.43 mmol) was added and the mixture allowed to stir for 2 h at 22 °C. At this time, ethylvinyl ether (~2mL) was added. The volatiles were removed under reduced pressure to provide a brown oil. Purification by silica gel column chromatography (50% ether/pentane) provided the cyclohexenol as a clear oil (244 mg, 2.43 mmol, >98%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.99-5.89 (2H, m), 4.17-3.71 (5H, m), 1.83 (1H, d, J = 9.6 Hz).

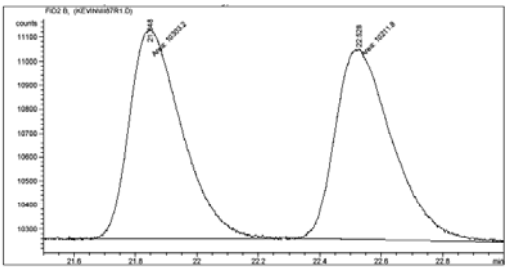
To a 50 mL round bottom flask charged with tetrapropylammonium perruthenate (TPAP) (68.0 mg, 0.193 mmol), 4-methylmorpholine *N*-oxide (NMO) (1.50 g, 12.8 mmol), and powdered 4Å MS (~1 g) was added CH_2Cl_2 (20 mL). The cyclohexenol (390 mg, 3.90 mmol) was added and the mixture allowed to stir at 22 °C. After ~7h, the mixture was passed through a short plug of silica gel (4 x 1 cm) eluted with Et_2O to afford **1.18** as an unstable clear oil (265 mg, 2.70 mmol, 69%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.11 (1H, tt, *J* = 10.4, 3.2 Hz), 6.19 (1H, tt, *J* = 10.4, 2.0 Hz), 4.38-4.37 (2H, m), 4.18 (2H, s).

Representative experimental procedure for Cu-catalyzed conjugate addition of dialkylzinc reagents to 2*H*-6*H*-pyran-3-one (1.18): (CAUTION: Me_2Zn IS PYROPHORIC! USE EXTREME CAUTION!) An oven-dried 13x100 mm test tube charged with **1.32** (4.4 mg, 0.0074 mmol) and $(CuOTf)_2 \bullet C_6H_6$ (1.5 mg, 0.0029 mmol), weighed out under a N_2 atmosphere in a glove box, was sealed with a septum and removed from the glove box. The cyclic enone (**1.18)** (14.7 mg, 0.150 mmol) was added as a solution in THF (1 mL), the reaction was allowed to cool to –30 °C and Me_2Zn (31.0 μL, 0.450 mmol) added. The reaction was allowed to stir at –30 °C for 6 h at which time the reaction was quenched by addition of a saturated solution of aqueous NH_4Cl (2 mL) then H_2O (2 mL). The aqueous layer was washed with Et_2O (2 x 4 mL). The combined organic layers were passed through a short plug of silica gel with Et_2O and the filtrate was concentrated *in vacuo* to provide a clear oil. Purification by silica gel

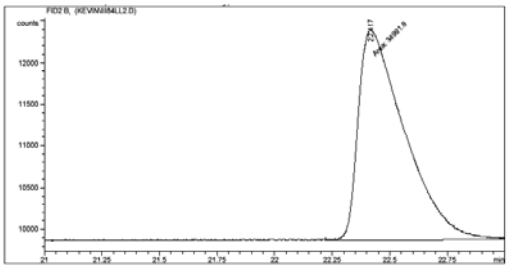
chromatography (15% diethyl ether/pentane) yielded **1.105** as a clear oil (10.0 mg, 0.087 mmol, 58.0%).

5-Methyl-dihydro-2*H*-pyran-3(4*H*)-one (1.105). IR (neat): 2949 (m), 2921 (s), 2847 (m), 1733 (m), 1716 (m), 1458 (m), 1372 (w), 1245 (w), 1106 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.04-3.86 (3H, m), 3.36 (1H, dd, *J* = 11.2, 8.8 Hz), 2.61 (1H, ddt, *J* = 16.0, 5.2, 1.6 Hz), 2.35-2.30 (1H, m), 2.11 (1H, dd, *J* = 16.0, 9.6 Hz), 0.99 (3H, d, *J* = 6.8 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 207.5, 74.5, 72.4, 46.2, 31.7, 17.7; **HRMS (ESI+):** Calcd for $C_6H_{10}O_2$: 114.0681, Found: 114.0683; **Optical Rotation:** $[\alpha]_D^{20}$ +8.48 (*c* 0.667, $CDCl_3$) for an enantiomerically enriched sample of >98% *ee*.

The enantiomeric purity of the conjugate addition product was established by



Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	21.848	MM	0.1975	1.03032e4	869.37445	50.22260
2	22.528	MM	0.2147	1.02118e4	792.82520	49.77740



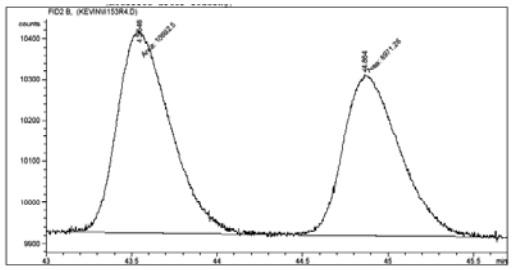
Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	22.417	MM	0.2319	3.49918e4	2515.32300	1.000e2

chiral GLC analysis (β-Dex column, 15 psi, 70 °C). Chromatograms are illustrated below:

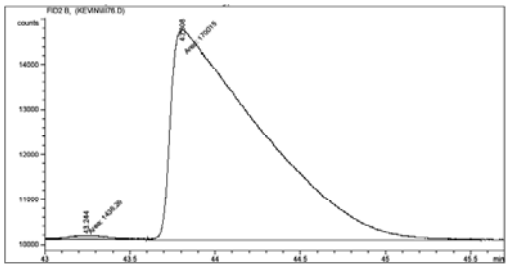
5-Ethyl-dihydro-2*H*-pyran-3(4*H*)-one (1.106). IR (neat): 2966 (s), 2921 (s), 2847 (s), 1737 (s), 1466 (m), 1417 (w), 1253 (m), 1175 (w), 1114 (m), 946 (w) cm^{-1}; **^{1}H NMR**

(400 MHz, $CDCl_3$): δ 4.04-3.87 (3H, m), 3.43 (1H, dd, *J* = 11.6, 8.4 Hz), 2.62 (1H, ddt, *J* = 15.6, 3.2, 1.2 Hz), 2.18-2.02 (2H, m), 1.48-1.25 (2H, m), 0.92 (3H, t, *J* = 7.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 207.9, 74.7, 70.8, 44.0, 38.0, 25.6, 11.2; **HRMS (ESI+):** Calcd. for $C_7H_{12}O_2$: 128.0837, Found: 128.0840; **Optical Rotation:** $[\alpha]_D^{20}$ +21.4 (*c* 0.820, $CHCl_3$) for an enantiomerically enriched sample of 98% *ee*.

The enantiomeric purity of the conjugate addition product was established by chiral GLC analysis (β-Dex column, 15 psi, 70 °C). Chromatograms are illustrated below:



Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	43.546	MM	0.3606	1.06925e4	494.16010	54.37674
2	44.864	MM	0.3806	8971.26270	392.83508	45.62326



Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	43.244	MM	0.3040	1436.25720	78.75166	0.83771
2	43.808	MM	0.6057	1.70015e5	4677.82178	99.16229

5-Ethyl-4-(hydroxy(phenyl)methyl)-2,2-dimethyl-dihydrofuran-3(2*H*)-one (1.115a). Relative configuration not determined. **IR (neat):** 3461 (br, s), 3067 (w), 3039 (w), 2984 (m), 2939 (m), 2878 (m), 1756 (s), 1506 (w), 1462 (m), 1384 (m), 1339 (w), 1234 (m), 1195 (m), 1117 (m), 1050 (m), 995 (m), 712 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37-7.26 (5H, m), 4.84 (1H, d, *J* = 8.0 Hz), 3.93 (1H, br s), 3.83-3.78 (1H, m), 2.56 (1H, dd, *J* = 9.6, 7.6 Hz), 1.28 (3H, s), 1.21-1.10 (1H, m), 1.14 (3H, s), 1.08-0.97 (1H, m), 0.78 (3H, t, *J* = 7.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 221.4, 140.5, 128.7, 128.6,

126.7, 80.4, 75.9, 74.0, 56.4, 27.0, 24.6, 22.1, 8.9; **HRMS (ESI+):** Calcd for $C_{15}H_{20}O_3$: 248.1412 Found: 248.1414.

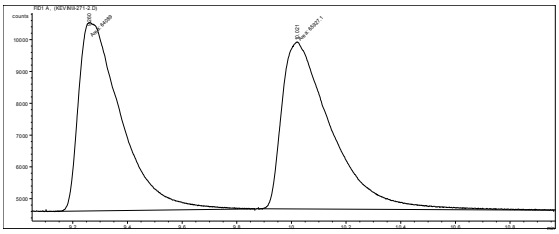
2-Ethyl-3-(hydroxy(phenyl)methyl)-2,3-dihydrochromen-4-one (1.113a). Analyzed as a 9:1 mixture of *trans-erythro* and *trans-threo* diastereomers. Major diastereomer: **IR (neat):** 3445 (bs, s), 3064 (w), 3042 (w), 2933 (w), 2884 (w), 1688 (s), 1612 (s), 1465 (s), 1323 (s), 1215 (m), 1144 (w), 1111 (w), 1035 (w), 1002 (w), 774 (m), 703 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.79 (1H, dd, *J* = 7.6, 1.6 Hz), 7.52-7.23 (6H, m), 7.02-6.94 (2H, m), 4.97 (1H, d, *J* = 8.8 Hz), 4.05-4.01 (1H, m), 2.71 (1H, dd, *J* = 9.2, 2.4 Hz), 1.84-1.72 (1H, m), 1.49-1.39 (1H, m), 0.83 (3H, t, *J* = 7.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 193.9, 159.2, 141.2, 136.8, 128.9, 128.6, 127.4, 127.0, 121.5, 120.3, 118.4, 79.9, 73.1, 58.2, 24.9, 10.0; **HRMS (ESI+):** Calcd for $C_{18}H_{18}O_3$: 282.1255 Found: 282.1265.

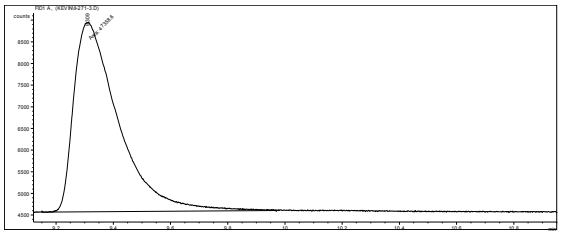
3-(Hydroxy(phenyl)methyl)-2-isopropyl-2,3-dihydrochromen-4-one (1.116a). Analyzed as a 9:1 mixture of *trans-erythro* and *trans-threo* diastereomers. Relative configuration not determined. Major diastereomer: **IR (neat):** 3454 (br), 3071 (w), 3034 (w), 2966 (m), 2935 (w), 2879 (w), 1704 (s), 1612 (s), 1463 (s), 1327 (s), 1228 (m), 1142 (w), 1111 (w), 1049 (m), 969 (w), 913 (w), 771 (w), 703 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.89 (1H, dd, *J* = 8.0, 2.0 Hz), 7.52-7.21 (6H, m), 7.00 (1H, td, *J* = 8.0, 0.8 Hz), 6.95 (1H, d, *J* = 8.8 Hz), 4.96 (1H, d, *J* = 9.2 Hz), 3.63 (1H, dd, *J* = 9.6, 2.0 Hz), 2.93 (1H, dd, *J* = 8.8, 2.0 Hz), 2.57 (1H, br s), 2.04-1.92 (1H, m), 0.85 (3H, *J* = 6.8 Hz),

0.73 (3H, d, J = 6.8 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 193.9, 159.4, 141.2, 136.8, 129.0, 128.7, 127.4, 127.0, 121.4, 120.7, 118.3, 84.2, 73.5, 56.1, 28.7, 19.1, 18.5; **HRMS (ESI+):** Calcd for $C_{19}H_{20}O_3$: 296.1412 Found: 296.1413.

5-Ethyl-2,2-dimethyl-dihydrofuran-3(2*H*)-one (1.115b). (Note: The general procedure for retroaldol fragmentation stated above is followed except the reaction is performed in a sealed tube due to product volatility.) **IR (neat):** 2970 (m), 2926 (m), 2873 (w), 1763 (s), 1734 (w), 1627 (w), 1457 (w), 1379 (w), 1184 (m), 1116 (m), 1014 (w), 985 (w), 698 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.10 (1H, dddd, J = 12.4, 10.0, 6.0, 6.0 Hz), 2.53 (1H, dd, J = 18.0, 6.0 Hz), 2.19 (1H, dd, J = 18.0, 10.0 Hz), 1.79-1.71 (1H, m), 1.68-1.57 (1H, m), 1.26 (3H, s), 1.19 (3H, s), 0.96 (3H, t, J = 7.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 218.3, 80.9, 74.2, 41.6, 28.9, 24.5, 21.9, 9.6; HRMS Calcd for $C_8H_{14}O_2$: 142.0994, Found: 142.0996; **Optical Rotation:** $[\alpha]_D^{20}$ +99.7 (*c* 0.413, $CHCl_3$) for an enantiomerically enriched sample of >98% *ee*.

The enantiomeric purity of the conjugate addition product was established by chiral GLC analysis (Chiraldex GTA column, 15 psi, 70°C) Chromatograms are illustrated below:





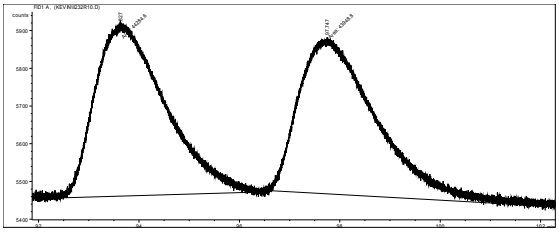
#	Time	Area	Height	Width	Area (%)
1	9.26	64423	5931.1	0.181	49.318

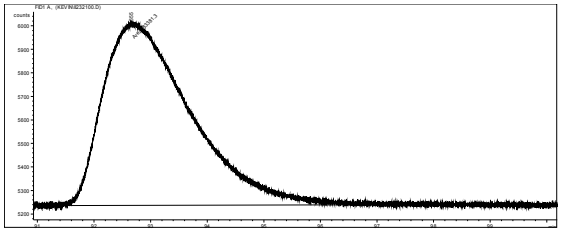
#	Time	Area	Height	Width	Area (%)
1	9.309	47358.6	4370	0.1806	100.00

2	10.021	65024.2	5251.8	0.2064	50.681

2-Ethyl-2,3-dihydrochromen-4-one (1.113b). IR (neat): 2965 (w), 2921 (w), 2878 (w), 1695 (s), 1608 (m), 1466 (s), 1316 (m), 1228 (w), 1150 (w), 1116 (w), 1028 (w), 956 (w), 873 9w), 766 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.86 (1H, dd, *J* = 7.6, 1.6 Hz), 7.47-7.43 (1H, m), 7.00-6.95 (2H, m), 4.40-4.33 (1H, m), 2.67 (2H, d, *J* = 8.4 Hz), 1.94-1.71 (2H, m), 1.06 (3H, t, *J* = 7.2 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 192.9, 161.9, 136.1, 127.1, 121.3, 121.2, 118.1, 79.2, 42.7, 28.1, 9.5; **Anal. Calcd for $C_{11}H_{12}O_2$:** C, 74.98; H, 6.86; Found: C, 75.11; H, 7.05; **Optical Rotation:** $[\alpha]_D^{20}$ +80.3 (*c* 0.093, $CHCl_3$) for an enantiomerically enriched sample of >98% *ee*.

The enantiomeric purity of the conjugate addition product was established by chiral GLC analysis (Chiraldex GTA column, 15 psi, 100 °C). Chromatograms are illustrated below:





#	Time	Area	Height	Width	Area (%)
1	93.627	44284.6	461.2	1.6005	49.739
2	97.747	43948.8	416	1.7607	50.260

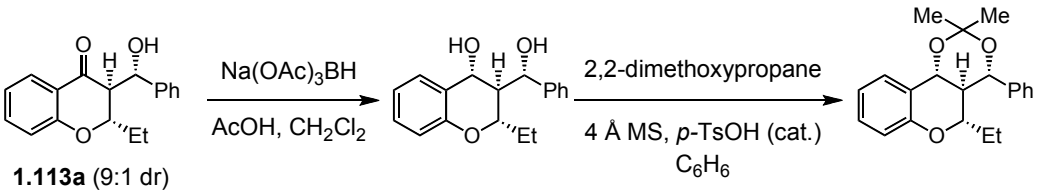
#	Time	Area	Height	Width	Area (%)
1	92.655	83381.3	782.6	1.7758	100.00

2-Isopropyl-2,3-dihydrochromen-4-one (1.116b). IR (neat): 2965 (w), 2926 (w), 2878 (w), 1695 (s), 1608 (m), 1462 (s), 1306 (m), 1233 (m), 1111 (w), 1028 (w), 887 (w), 761

(m), 664 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.88-7.84 (1H, m), 7.47-7.42 (1H, m), 6.99-6.95 (2H, m), 4.17 (1H, ddd, *J* = 12.4, 6.0, 3.6 Hz), 2.73-2.60 (2H, m), 2.04 (1H, qqd, *J* = 13.6, 6.8, 6.8 Hz), 1.06 (3H, d, *J* = 6.8 Hz), 1.03 (3H, d, *J* = 6.8 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 193.2, 162.1, 136.0, 127.0, 121.2, 121.1, 118.0, 82.6, 40.2, 32.3, 18.0, 17.9; **HRMS (ESI+):** Calcd for $C_{12}H_{15}O_2$ ($M+H^+$): 191.1076, Found: 191.1072; **Optical Rotation:** $[\alpha]_D^{20}$ +49.6 (*c* 0.433, $CHCl_3$) for an enantiomerically enriched sample of 91% *ee*.

The enantiomeric purity of the conjugate addition product was established by chiral HPLC analysis (Chiralpak AS column, 98:2 hexanes/*i*PrOH, t_{minor} = 5.5 min, t_{major} = 6.0 min).

ν The following sequence was carried out to determine of relative stereochemistry of 1.113a.



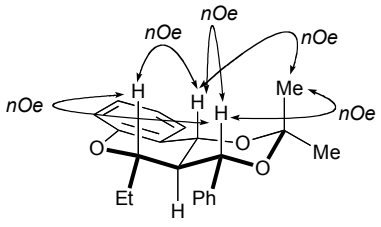
1.113a (9:1 dr)

Dimethylacetal: To a flask charged with $Na(OAc)_3BH$ (21.0 mg, 0.0991 mmol), CH_2Cl_2 (2.0 mL) followed by HOAc (40.0 μL, 0.699 mmol) were added. To this solution, **1.113a** (25.0 mg, 0.0886 mmol, 9:1 dr) dissolved in CH_2Cl_2 (2.0 mL) was added and the mixture was allowed to stir at 22 °C for 24 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (2 mL) and the resulting mixture washed with CH_2Cl_2 (3 x

2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (10% EtOAc/pentane) provided the diol as a clear oil (8.0 mg, 0.028 mmol, 33% yield, 50% conv, >30:1 dr). **IR (neat):** 3360 (br), 2988 (m), 2931 (m), 1719 (w), 1616 (m), 1588 (m), 1491 (s), 1462 (s), 1228 (s), 1136 (w), 1062 (m), 987 (m), 759 (s), 713 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.44-7.31 (6H, m), 7.20 (1H, dt, *J* = 8.0, 1.6 Hz), 6.97 (1H, dt, *J* = 7.2, 1.2 Hz), 6.86 (1H, dd, *J* = 8.4, 1.2 Hz), 5.17 (1H, d, *J* = 4.4 Hz), 4.71 (1H, d, *J* = 8.4 Hz), 3.80 (1H, ddd, *J* = 8.8, 4.4, 4.4 Hz), 2.32 (1H, dt, *J* = 8.4, 4.8 Hz), 2.20 (1H, br s), 1.80-1.69 (1H, m), 1.62-1.52 (1H, m), 0.87 (3H, t, *J* = 7.2 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 152.8, 142.8, 129.3, 129.2, 129.0, 128.4, 126.7, 124.9, 121.3, 117.4, 74.6, 65.3, 50.9, 26.0, 14.3, 10.3; **HRMS (ESI+):** Calcd for $C_{18}H_{20}O_3$: 284.1412, Found: 284.1412.

Dimethylacetal from 1.113a: To a flame dried one dram vial containing 4Å MS (small spatula tip) was added the diol (6.0 mg, 0.021 mmol) dissolved in benzene (800 μL). To this vial *p*-TsOH (one small crystal) and 2,2 dimethoxypropane (5.9 μL, 0.047 mmol) were added and the mixture allowed to stir at 22°C for 20 min. At this time the solution was passed through a short plug of silica eluting with EtOAc. The filtrate was concentrated *in vacuo*. Purification by silica gel chromatography (1% EtOAc/Pentane) afforded the desired dimethylacetal as a colorless oil (>30:1 d.r.). **IR (neat):** 2995 (m), 2924 (m), 2904 (m), 1618 (w), 1588 (w), 1492 (s), 1462 (s), 1386 (s), 1260 (s), 1210 (s), 1129 (m), 1084 (s), 1013 (m), 968 (m), 902 (m), 766 (s), 710 (m), 675 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40-7.30 (6H, m), 7.14 (1H, tq, *J* = 7.6, 0.8 Hz), 6.94 (1H,

td, J = 7.6, 1.2 Hz), 6.77 (1H, dd, J = 8.4, 1.2 Hz), 4.99 (1H, d, J = 10.0 Hz), 4.76 (1H, d, J = 10.0 Hz), 4.00-3.95 (1H, m), 1.99 (1H, q, J = 10.0 Hz), 1.69 (3H, s), 1.57 (3H, s), 1.31-1.16 (1H, m), 0.88-0.76 (1H, m), 0.65 (3H, t, J = 7.2 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 153.6, 140.3, 128.9, 128.8, 128.5, 128.1, 125.8, 123.8, 120.8, 116.5, 100.1, 67.9, 46.4, 34.3, 30.4, 29.9, 27.8, 20.0, 9.4; **HRMS (ESI+):** Calcd for $C_{21}H_{24}O_3$: 324.1725, Found: 324.1719.



ν Representative experimental procedure for three-component *in situ* generation of catalyst for conjugate addition of dialkylzinc reagents to unsaturated lactones with benzaldehyde *in the presence of CuCl and CuI*: (CAUTION: Et_2Zn IS PYROPHORIC! USE EXTREME CAUTION!) An oven-dried 13x100 mm test tube was charged with **1.32** (8.9 mg, 0.0150 mmol) and CuCl (1.17 mg, 0.0118 mmol). The test tube was sealed with a septum and purged with N_2. Toluene (1.0 mL) was added followed by 5,6-dihydro-2*H*-pyran-2-one (**1.1**) (13.0 μL, 0.150 mmol) and benzaldehyde (29.0 μL, 0.300 mmol). The mixture was allowed to cool to –30 °C and Et_2Zn (46.0 μL, 0.450 mmol) was added. The mixture was allowed to stir at –30 °C for 12 h at which time the reaction was quenched upon addition of a saturated solution of aqueous NH_4Cl (1 mL) then H_2O

(1 mL). The aqueous layer was washed with EtOAc (2 x 2 mL). The combined organic layers were passed through a short plug of silica gel (4 x 1 cm) eluted with EtOAc and the filtrate was concentrated *in vacuo*. Purification by silica gel column chromatography (30% diethyl ether/hexanes) afforded a clear oil (18.1 mg, 0.0773 mmol, 51%). The general procedure for PCC oxidation was followed to provide **1.93b** as a clear oil (15.7 mg, .0680 mmol, 87.5%).

ν Representative experimental procedure for preparation of peptide-CuCl and peptide-CuI complexes: An oven-dried 13x100 mm test tube was charged with CuCl (9.89 mg, 0.100 mmol) and **1.32** (59.2 mg, 0.100 mmol) in air. The test tube was sealed with a septum, purged with N_2, and CH_2Cl_2 (4 mL) was added. The reaction was allowed to stir at 22 °C for 12 h and which time the orange solution was filtered through filter paper and concentrated to afford an orange solid. The orange solid (**1.118**) could either be used for catalytic ACA, without further purification, by dissolving in toluene (0.012 N) or triturated from CH_2Cl_2/pentane and used as a pale orange powder (51.1 mg, 0.739 mmol, 73.9%)

CuI-1.32-complex (1.117). IR (neat): 3307 (bs m), 3049 (m), 2967 (s), 2923 (m), 2873 (m), 1658 (s), 1532 (m), 1438 (m), 1262 (w), 1092 (w), 771 (m), 695 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.68 (1H, br s); 7.77 (1H, br s), 7.51-7.13 (18H, m), 6.91 (1H, t, *J* = 7.6 Hz), 6.06 (1H, br s), 4.53 (1H, br q, *J* = 6.8 Hz), 4.05 (1H, br s), 3.09-2.99 (3H, br s), 2.15 (1H, br s), 1.68 (1H, br s), 1.30-1.19 (3H, m), 1.12-1.03 (2H, m), 0.73 (3H, t, *J* =

7.2 Hz), 0.60-0.45 (6H, br s); **^{31}P NMR (162 MHz, $CDCl_3$):** δ -14.67; **HRMS (ESI+):** Calcd for $C_{37}H_{42}ICuN_3O_2PNa$ (M+Na): 804.1253, Found: 804.1260.

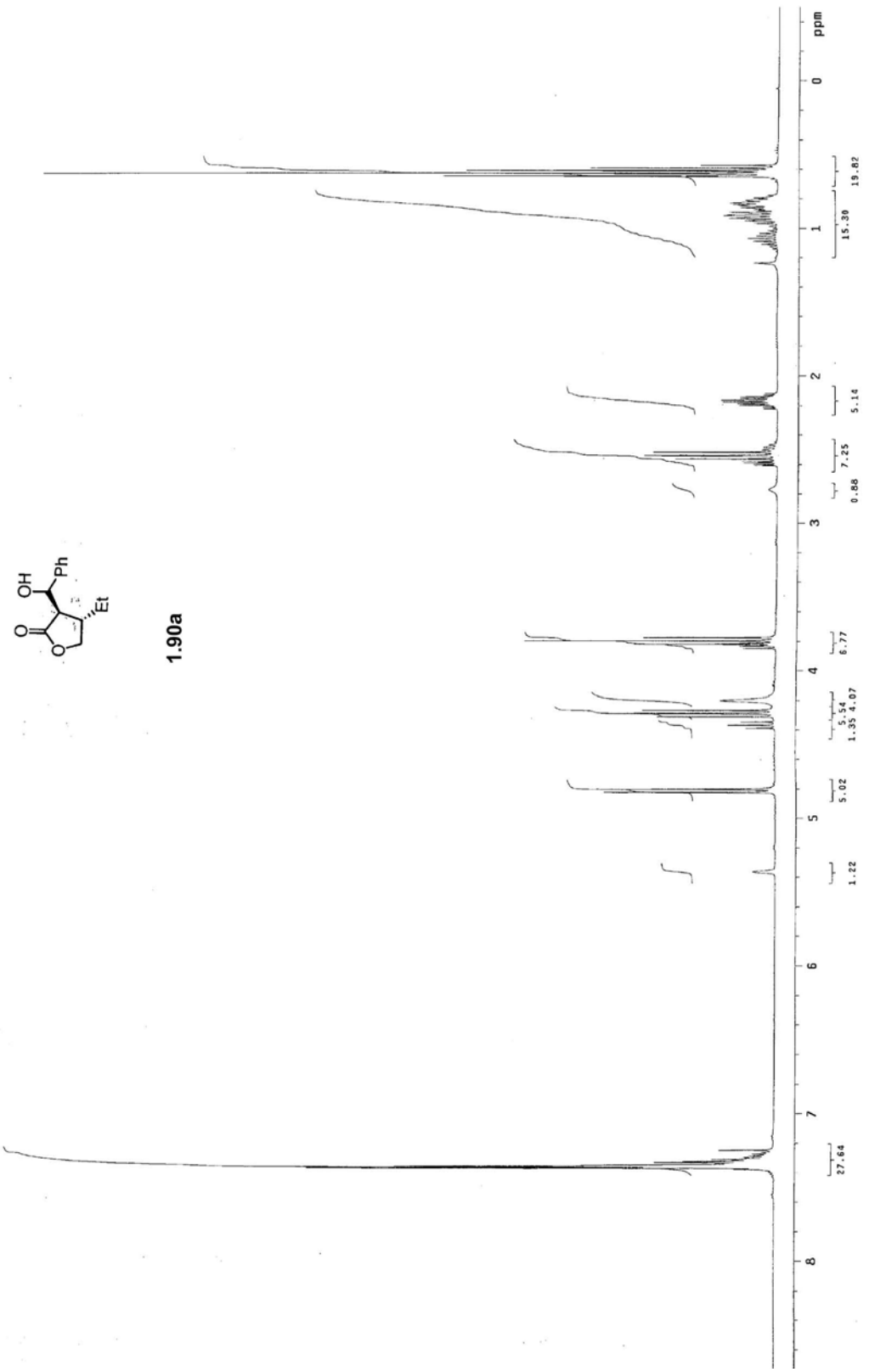
CuCl-1.32-complex (1.117). mp: 108-115 (dec.); **IR (neat):** 3301 (br s), 3056 (w), 2959 (m), 2925 (m), 2862 (w), 1654 (s), 1523 (m), 1437 (m), 1375 (w), 1266 (w), 1227 (w), 1101(w), 1033 (w), 753 (m), 696 (s), 668 (w), 520 (bs w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.45 (1H, br s), 7.92 (1H, br s), 7.60-7.01 (19 H, br m), 6.41 (1H, br s), 4.60 (1H, br s), 3.67 (1H, br s), 3.24-3.02 (4H, br m), 2.35 (1H, br s), 1.25-1.17 (2H, br m), 1.12-1.02 (2H, br m), 0.64 (3H, t, *J* = 7.2 Hz), 0.45 (3H, br d, *J* = 5.2 Hz), 0.41 (3H, br d, *J* = 5.6 Hz); **^{31}P NMR (162 MHz, $CDCl_3$):** δ -11.37; **HRMS (ESI+):** Calcd for $C_{37}H_{42}ClCuN_3O_2PNa$ (M+Na): 712.1897, Found: 712.1891.

CuCl-1.38-complex (1.120). IR (neat): 3312 (br), 3057 (w), 2965 (m), 2927 (m), 2867 (w), 1652 (s), 1511 (s), 1376 (m), 1245 (m), 1164 (m), 1099 (w), 893 (w), 746 (m), 692 (m), 508 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.87 (br s), 7.87 (br s), 7.54-7.24 (br m), 7.11 (br s), 6.84 (br s), 6.34 (br s), 4.66 (br s), 3.70 (br s), 3.06 (br s), 1.26 (br s), 1.06 (br s), 0.69 (br s), 0.60 (br s); **^{31}P NMR (162 MHz, $CDCl_3$):** δ -8.19; **LRMS:** Calcd for $C_{37}H_{42}ClCuN_3O_2PNa$ (M+Na): 798.26, Found: 798.31; **Optical Rotation:** $[\alpha]_D^{20}$ –107 (*c* 0.533, $CHCl_3$).

CuCN-1.32-complex (1.119). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (1H, br s), 7.67 (1H, br s), 7.45 (1H, t, *J* = 7.6 Hz), 7.35-7.14 (17H, m), 6.89 (1H, t, *J* = 7.6 Hz), 6.46 (1H, br

s), 4.65 (1H, br s), 3.66 (1H, d, J = 6.0 Hz), 3.16-2.95 (1H, m), 2.20 (1H, br s), 1.79 (1H, br s), 1.28-1.21 (1H, m), 1.14-1.05 (1H, m), 0.76 (3H, t, J = 7.2 Hz), 0.63 (3H, d, J = 5.6 Hz), 0.57 (3H, d, J = 4.8 Hz); **^{31}P NMR (162 MHz, $CDCl_3$):** δ -11.4

ν Representative experimental procedure for three-component Cu-catalyzed conjugate addition of dialkylzinc reagents to unsaturated lactones with benzaldehyde promoted by CuI or CuCl complexes: (CAUTION: Et_2Zn IS PYROPHORIC! USE EXTREME CAUTION!) An oven-dried 13x100 mm test tube was charged with **1.117** (8.27 mg, 0.0120 mmol). The test tube was sealed with a septum and purged with N_2. Toluene (1.0 mL) was added followed by 5,6-dihydro-2*H*-pyran-2-one (**1.1**) (13.0 μL, 0.150 mmol) and benzaldehyde (29.0 μL, 0.300 mmol). The mixture was allowed to cool to –30 °C and Et_2Zn (46.0 μL, 0.450 mmol) was added. The mixture was allowed to stir at –30 °C for 12 h, at which time the reaction was quenched upon addition of a saturated solution of aqueous NH_4Cl (1 mL) then H_2O (1 mL). The aqueous layer was washed with EtOAc (2 x 2 mL). The combined organic layers were passed through a short plug of silica gel eluted with EtOAc and the filtrate was concentrated in vacuo. Purification by silica gel column chromatography (30% diethyl ether/hexanes) afforded a clear oil (30.4 mg, 0.130 mmol, 87%). The general procedure for PCC oxidation was followed to provide **1.93b** as a clear oil (26.4 mg, 0.114 mmol, 87%).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4
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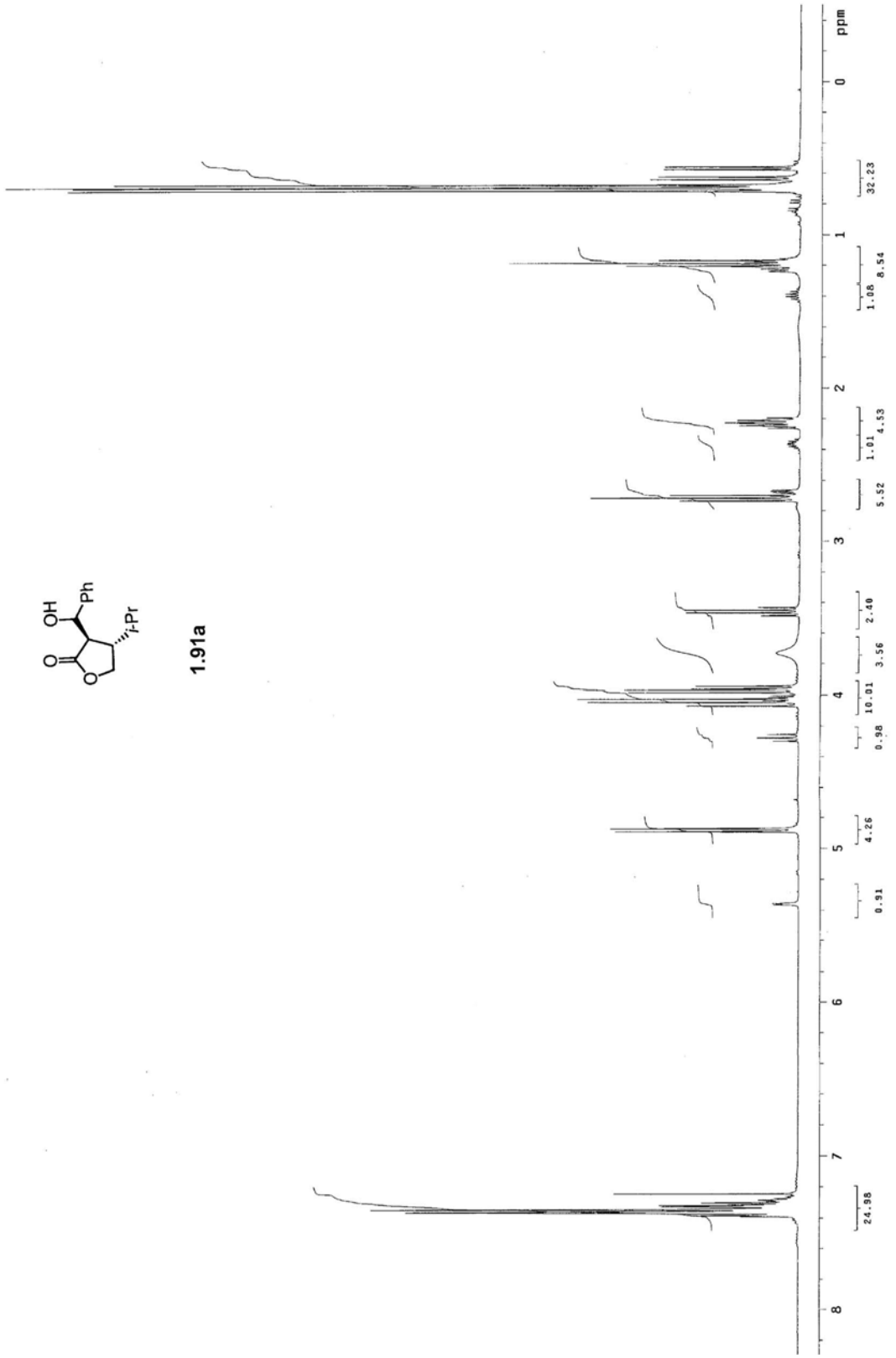
1.35
4.07
5.02
1.22
27.64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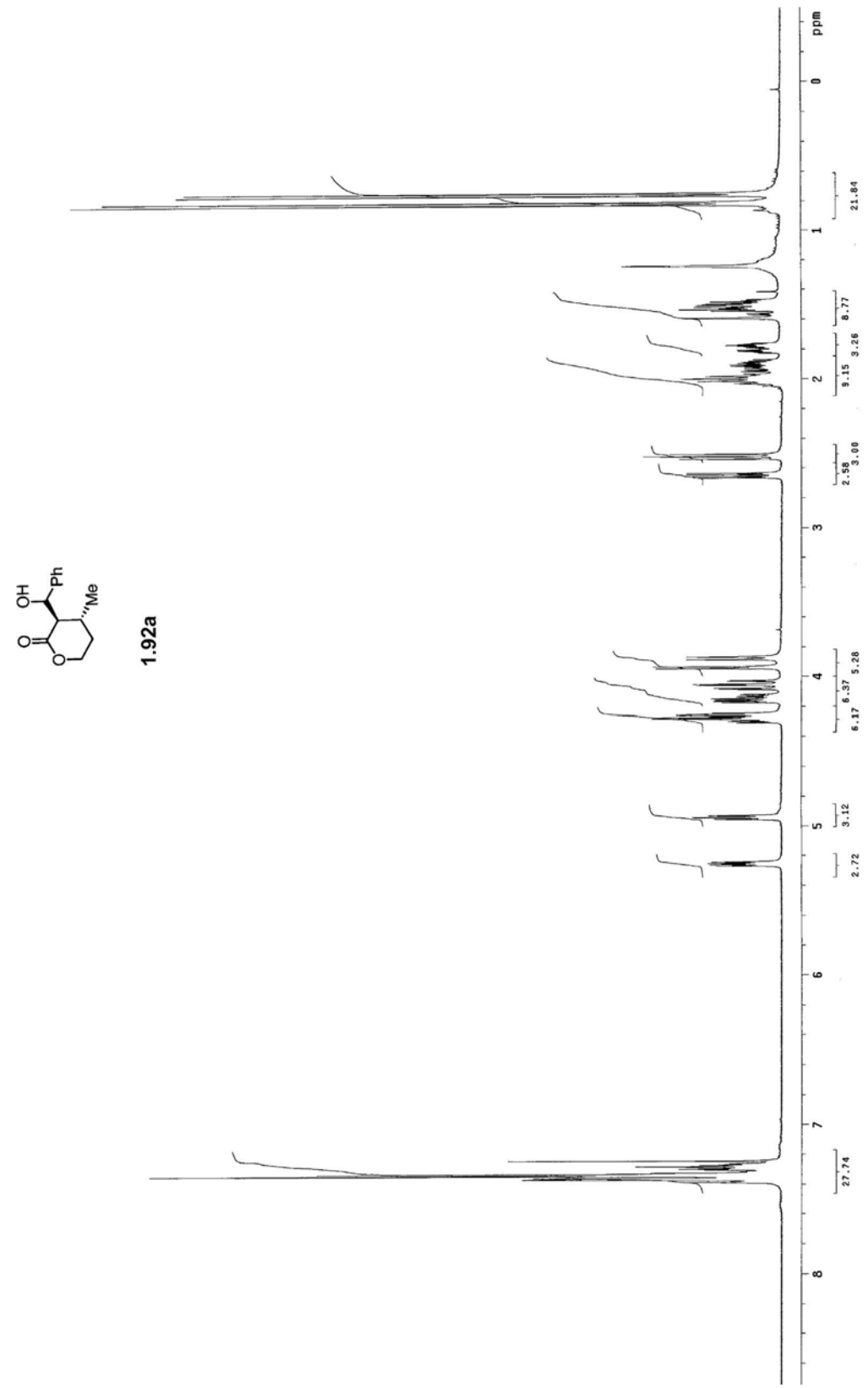
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3.12
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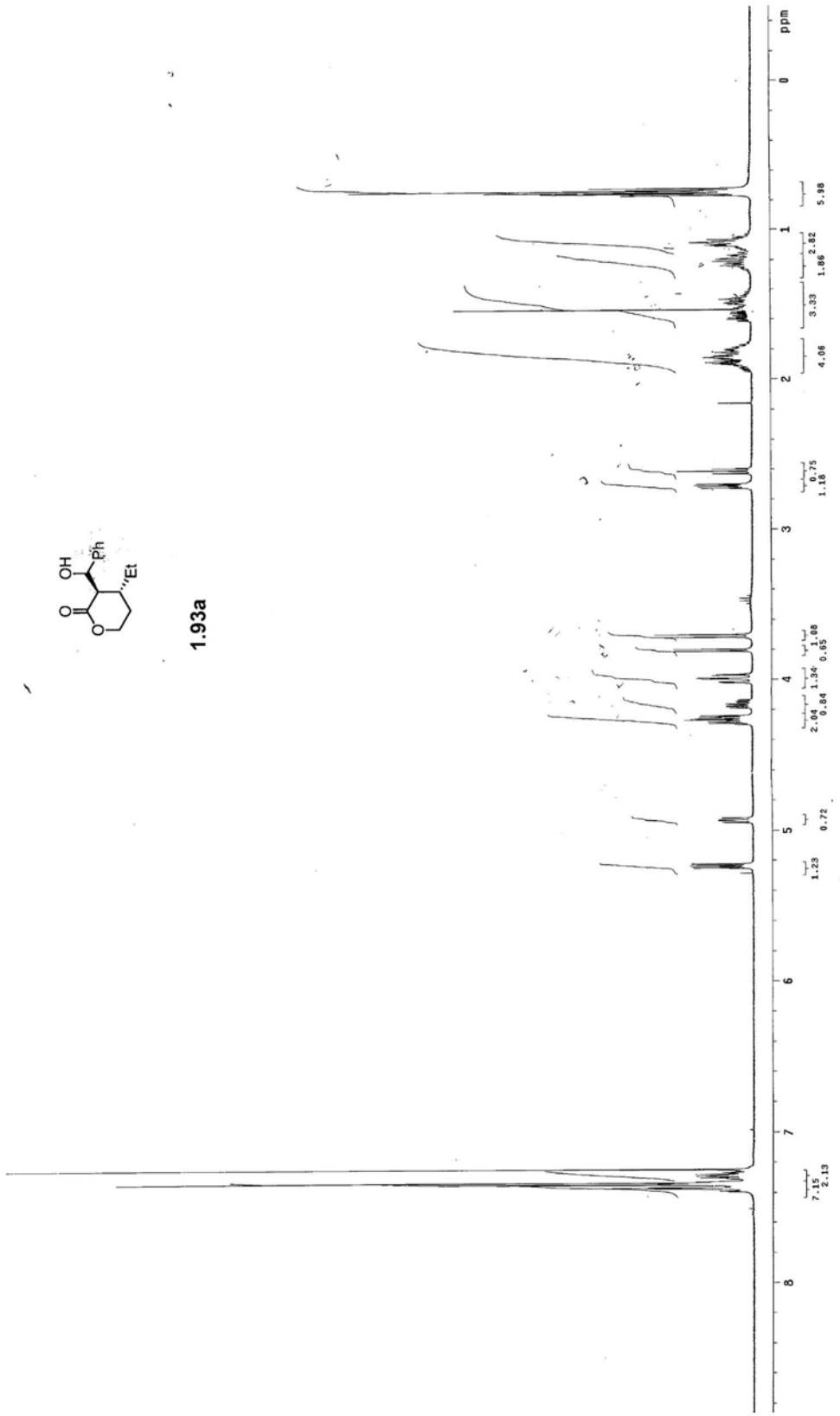
27.74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1.23
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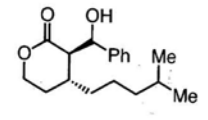
5.98



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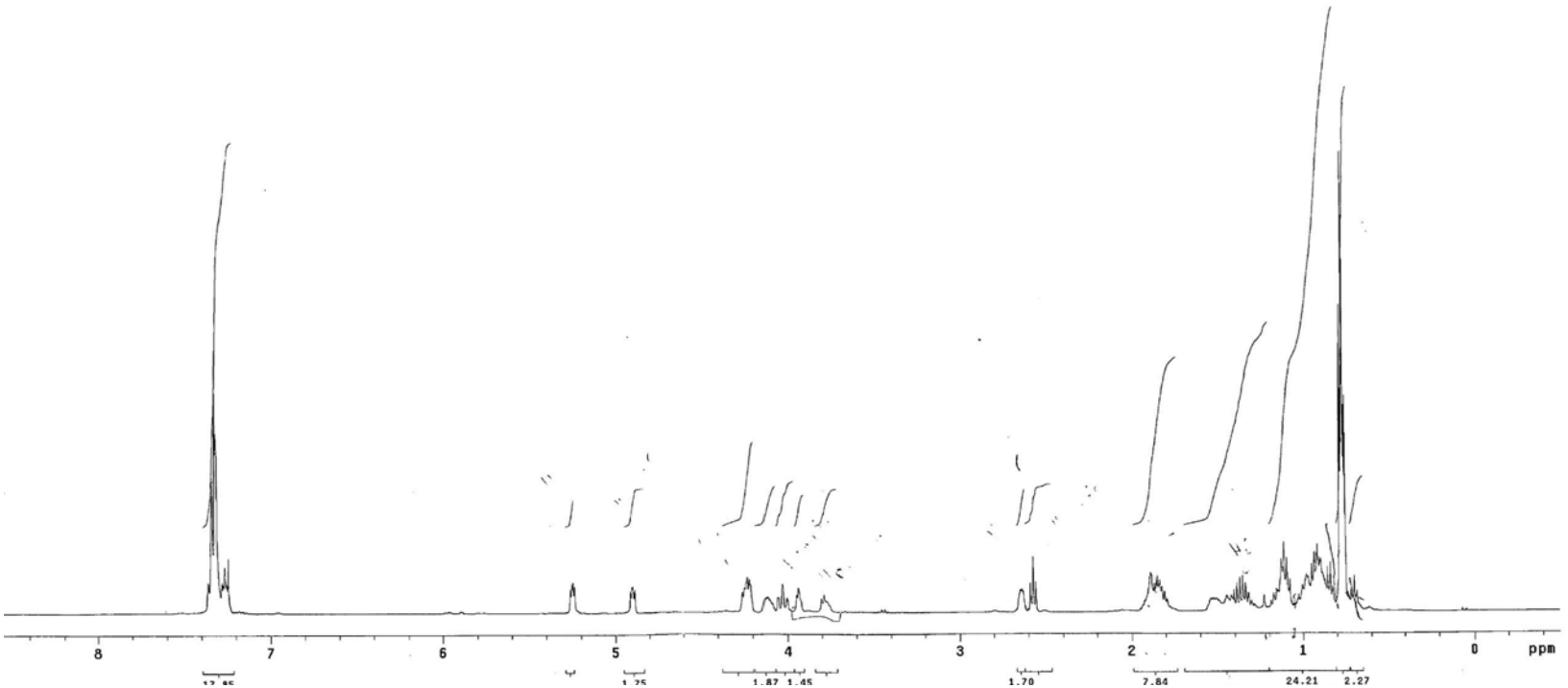

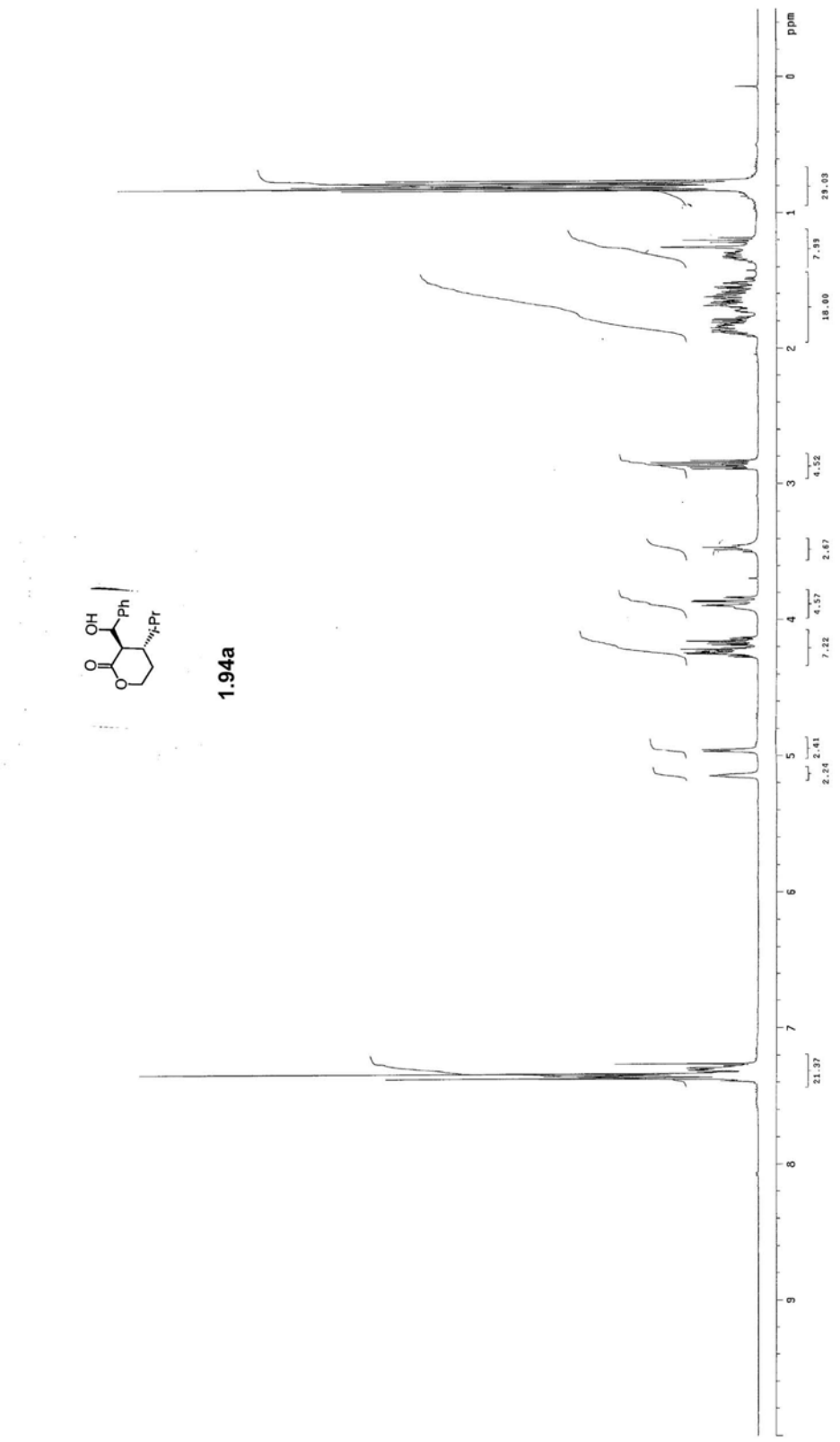
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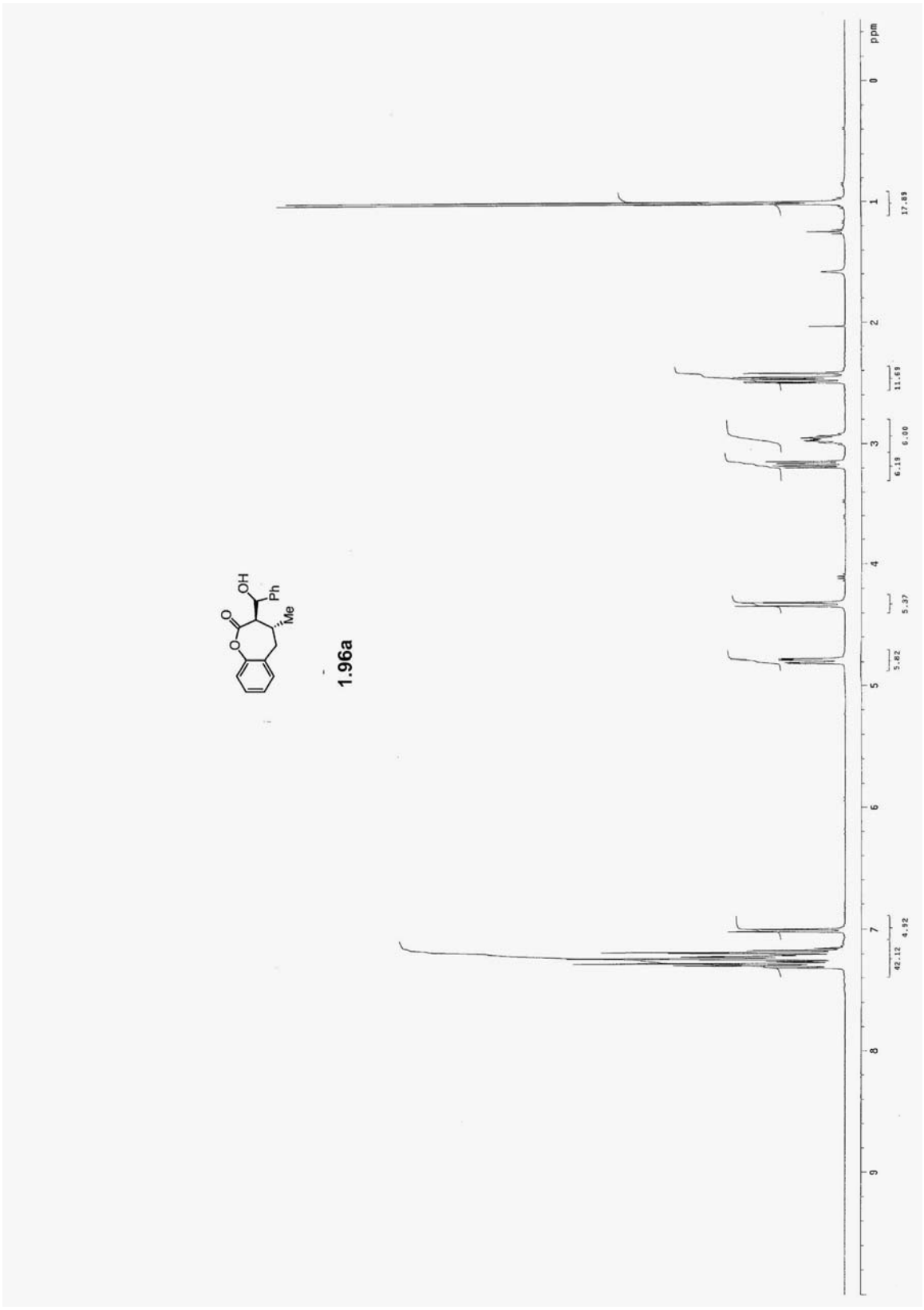
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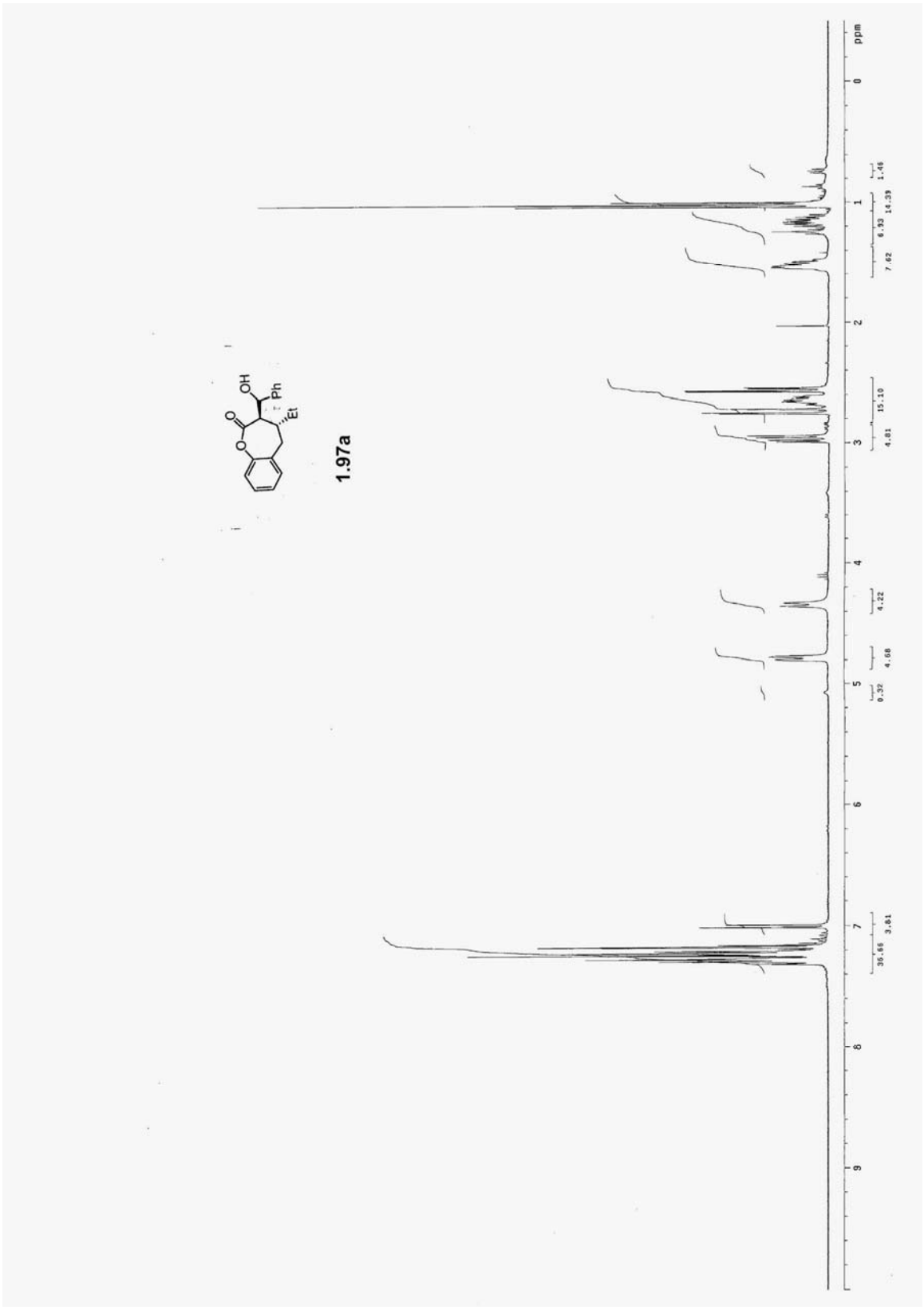
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8
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15.10
4.81
4.22
4.68
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36.66
3.81

Ph
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Et
O
O
1.90b
ppm
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2
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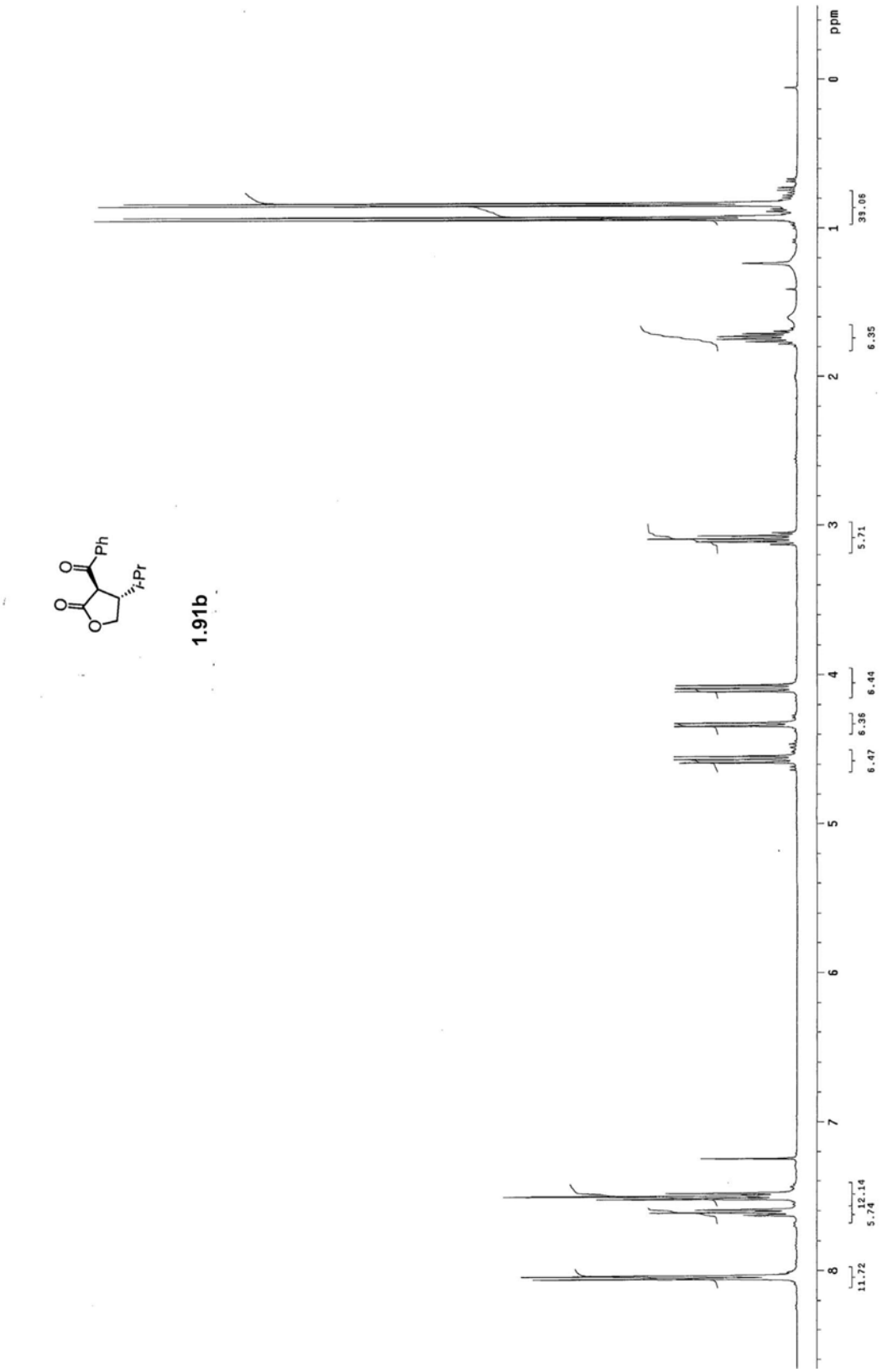
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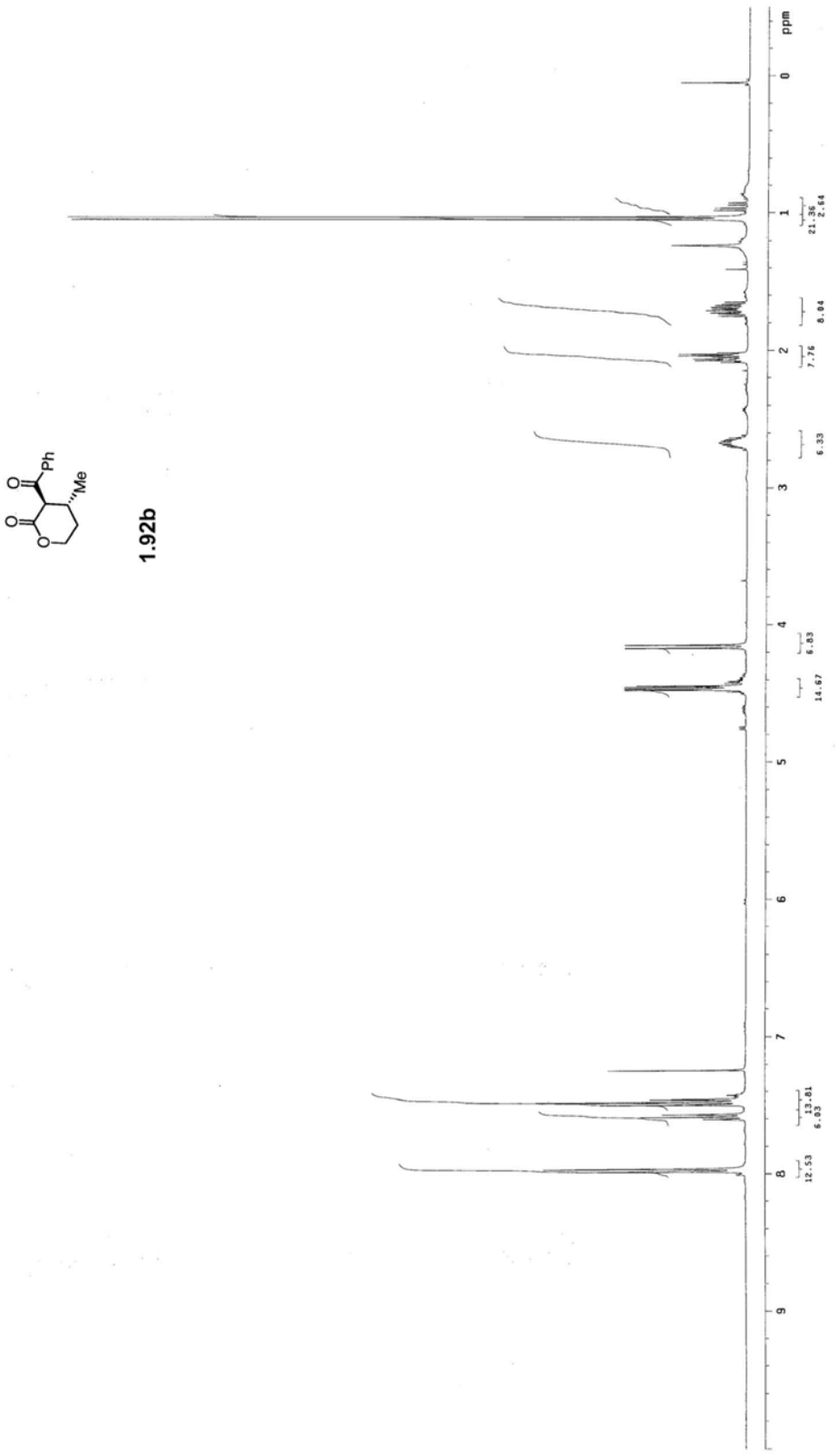
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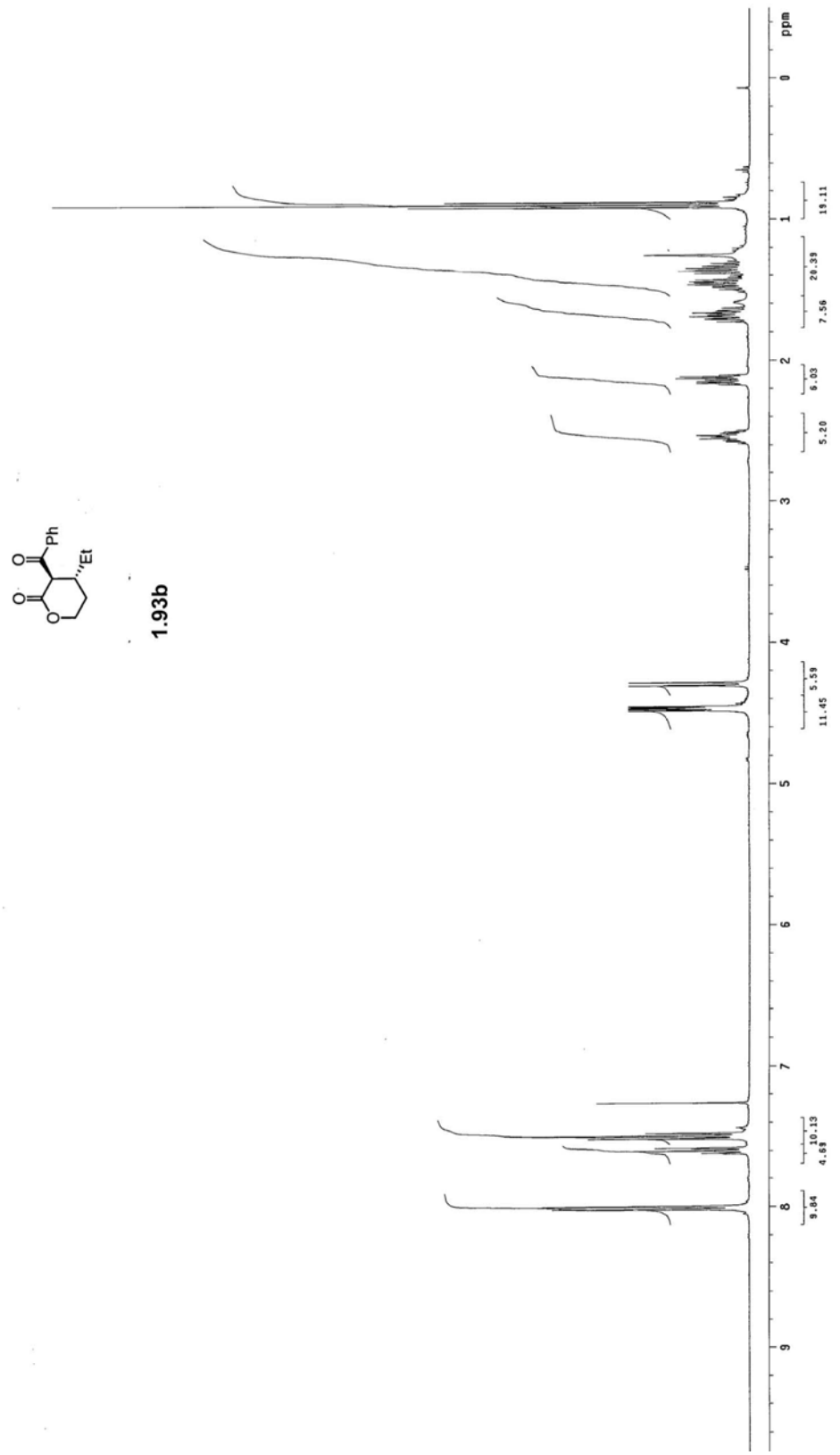
6.03
12.53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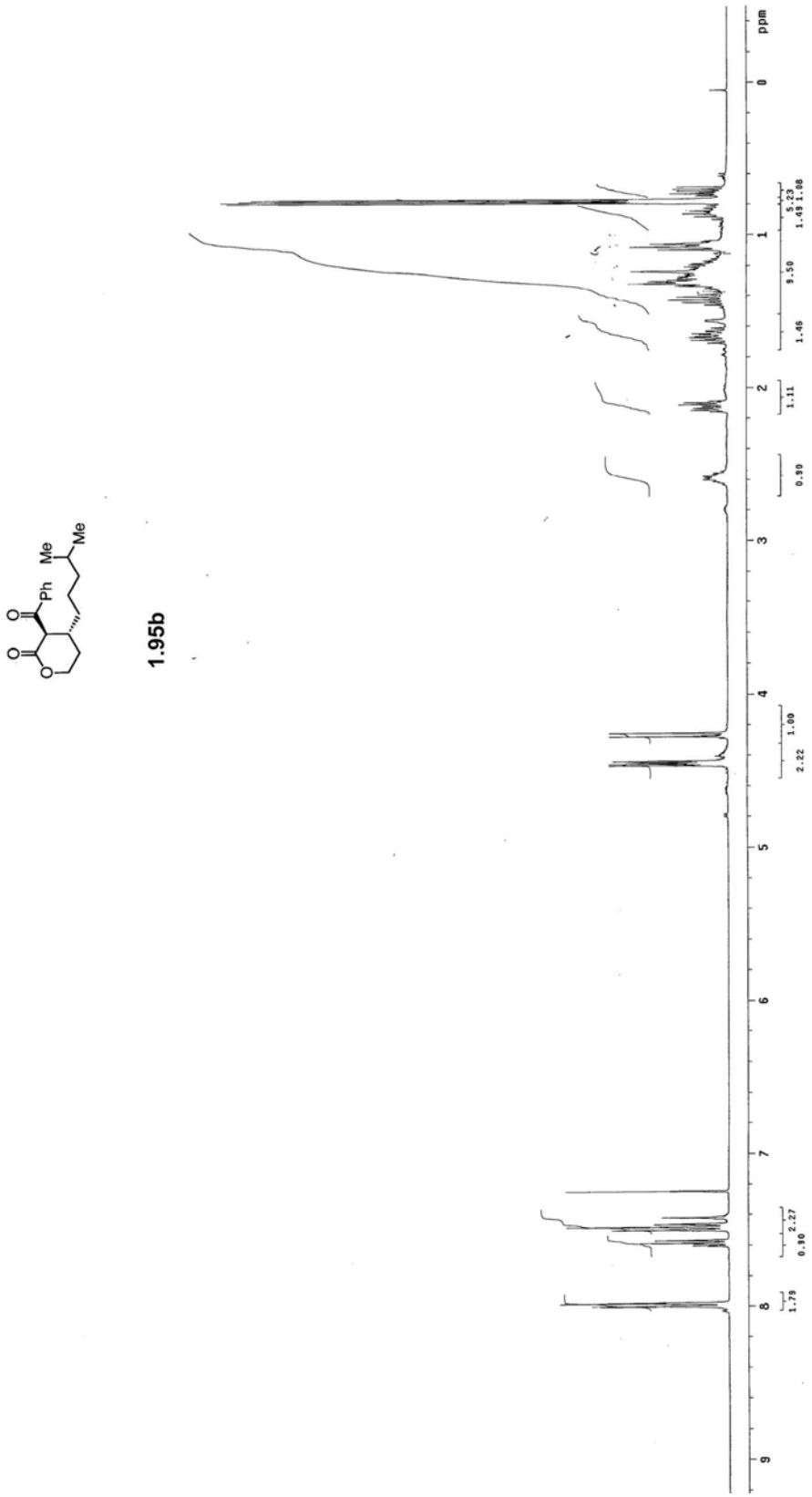
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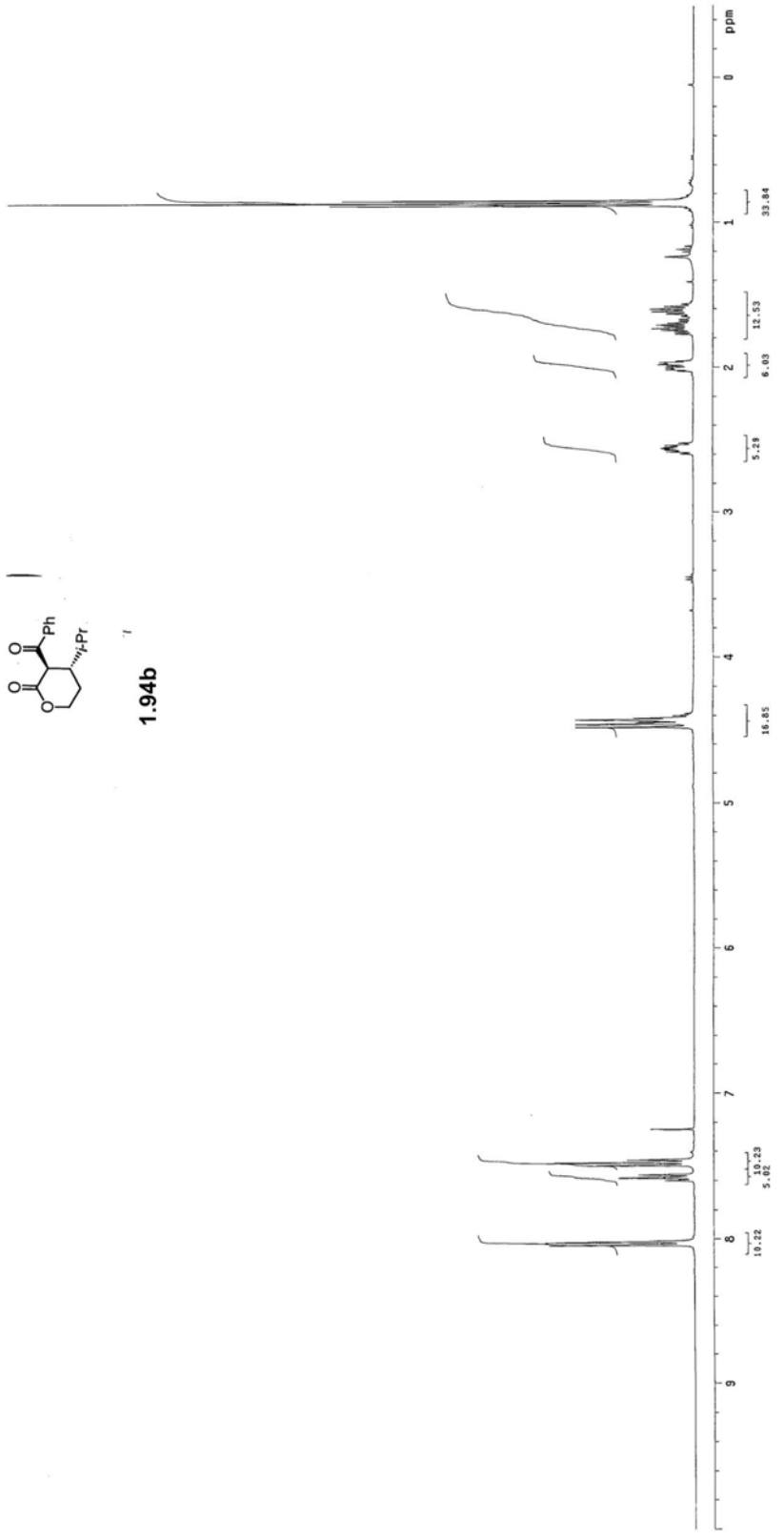
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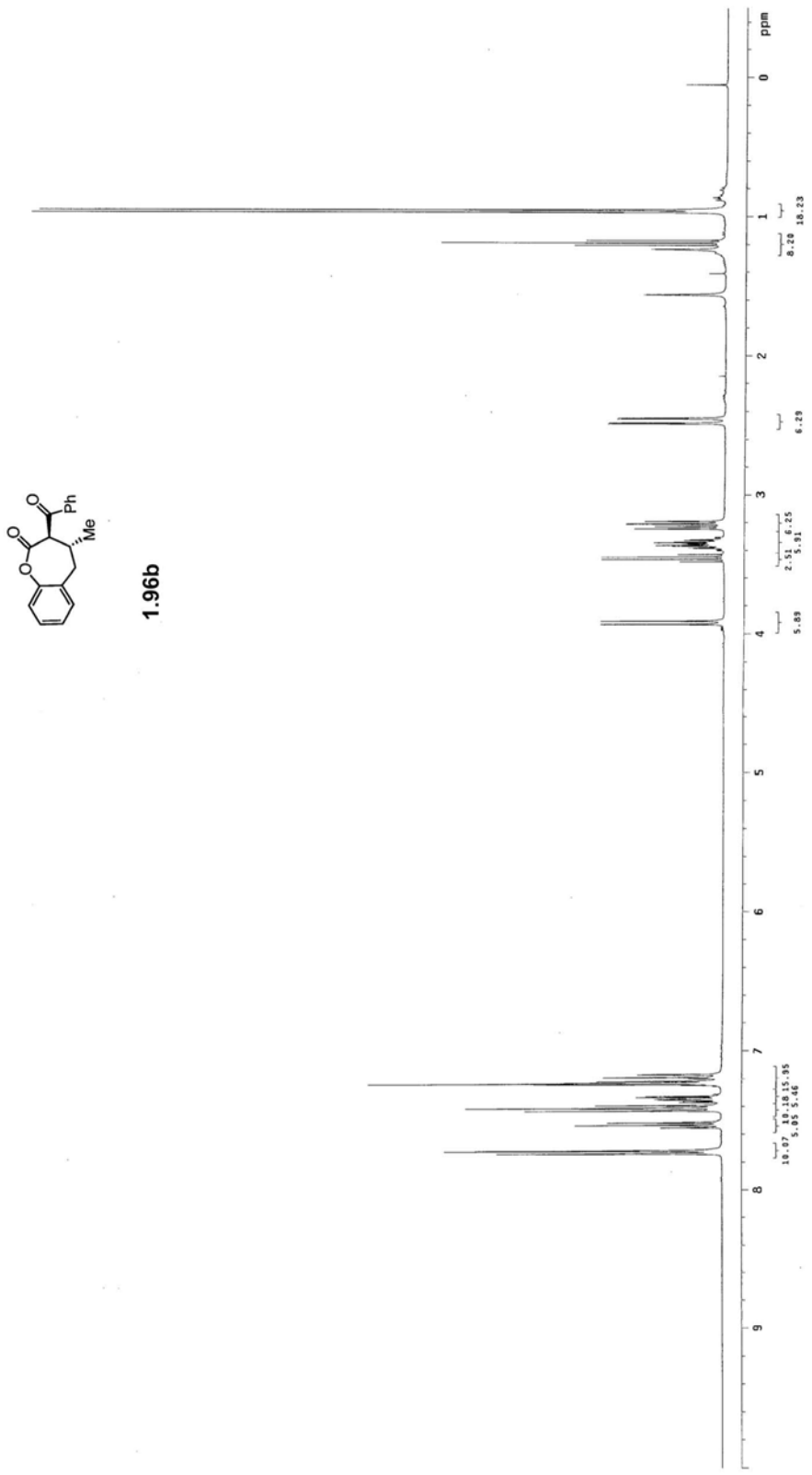
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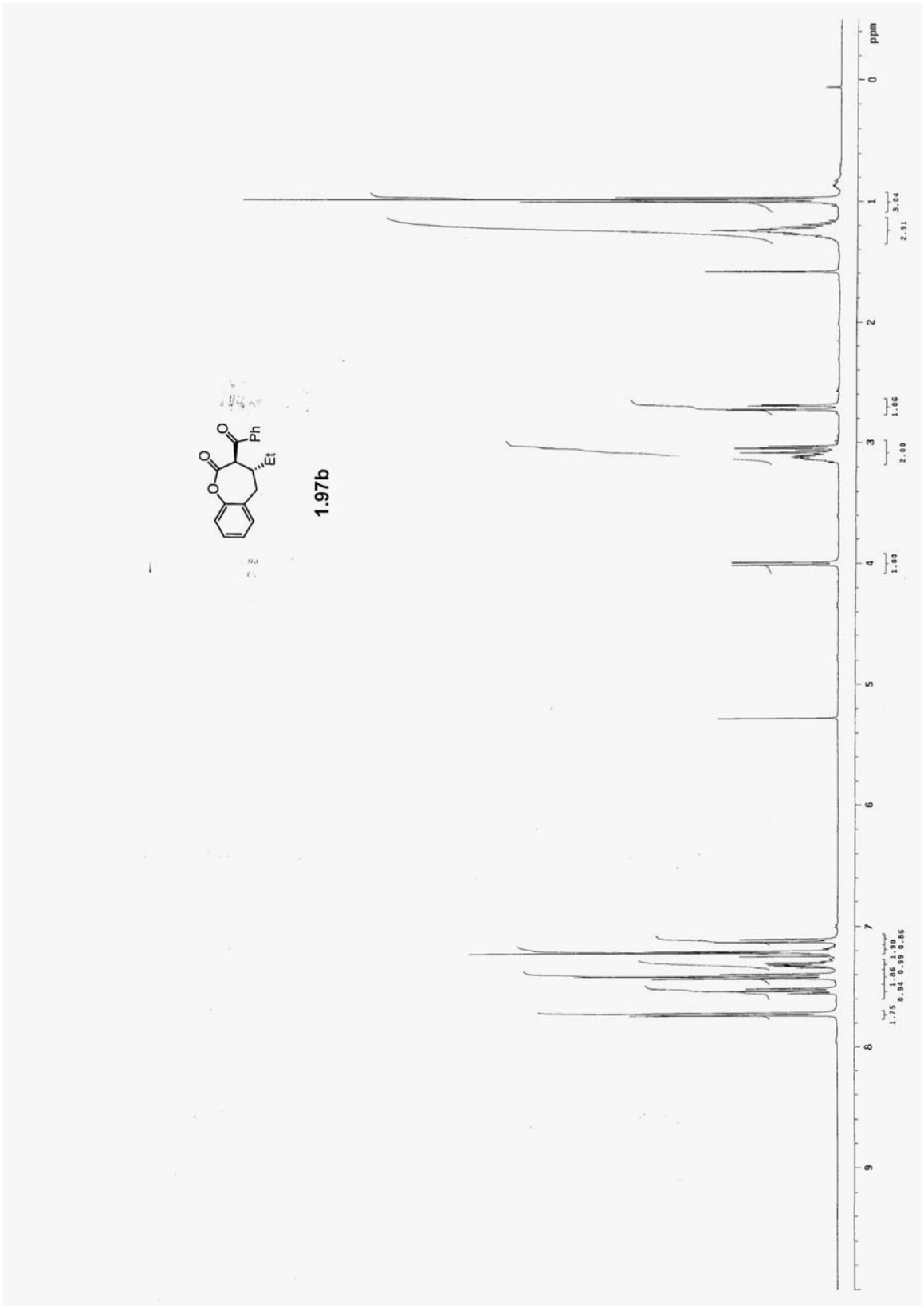
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Et
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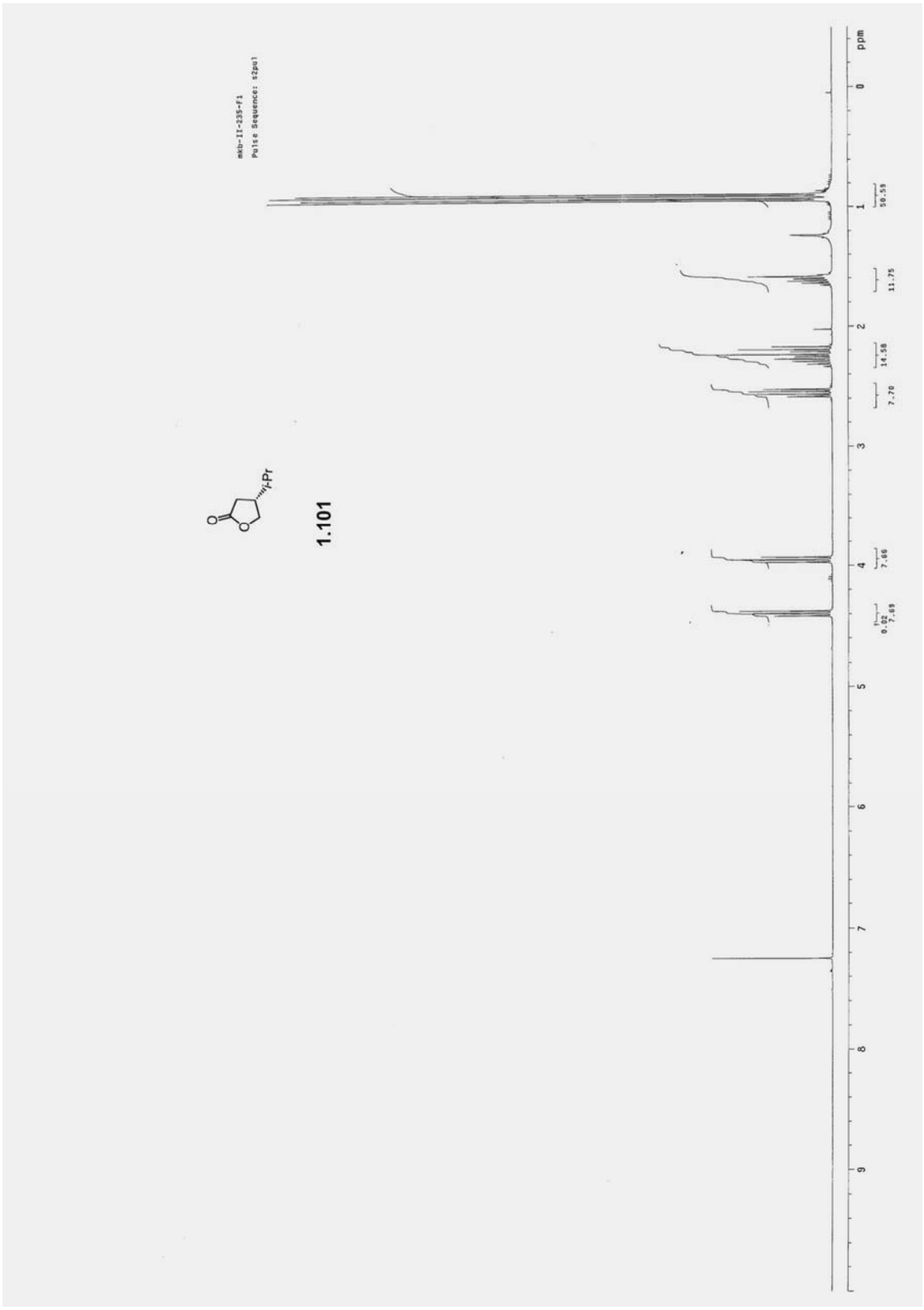
ppm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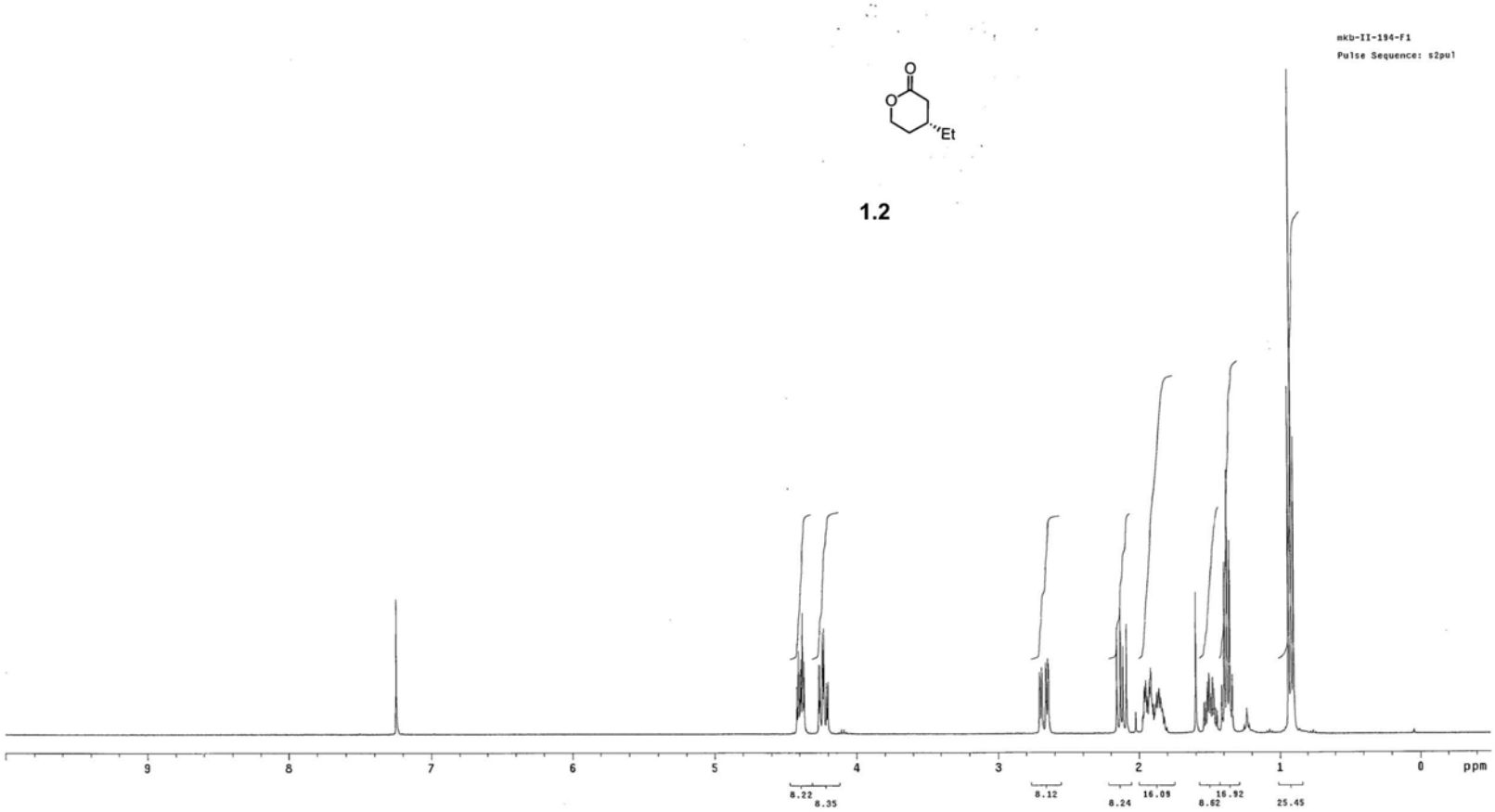
7.69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8
7
6
5
4
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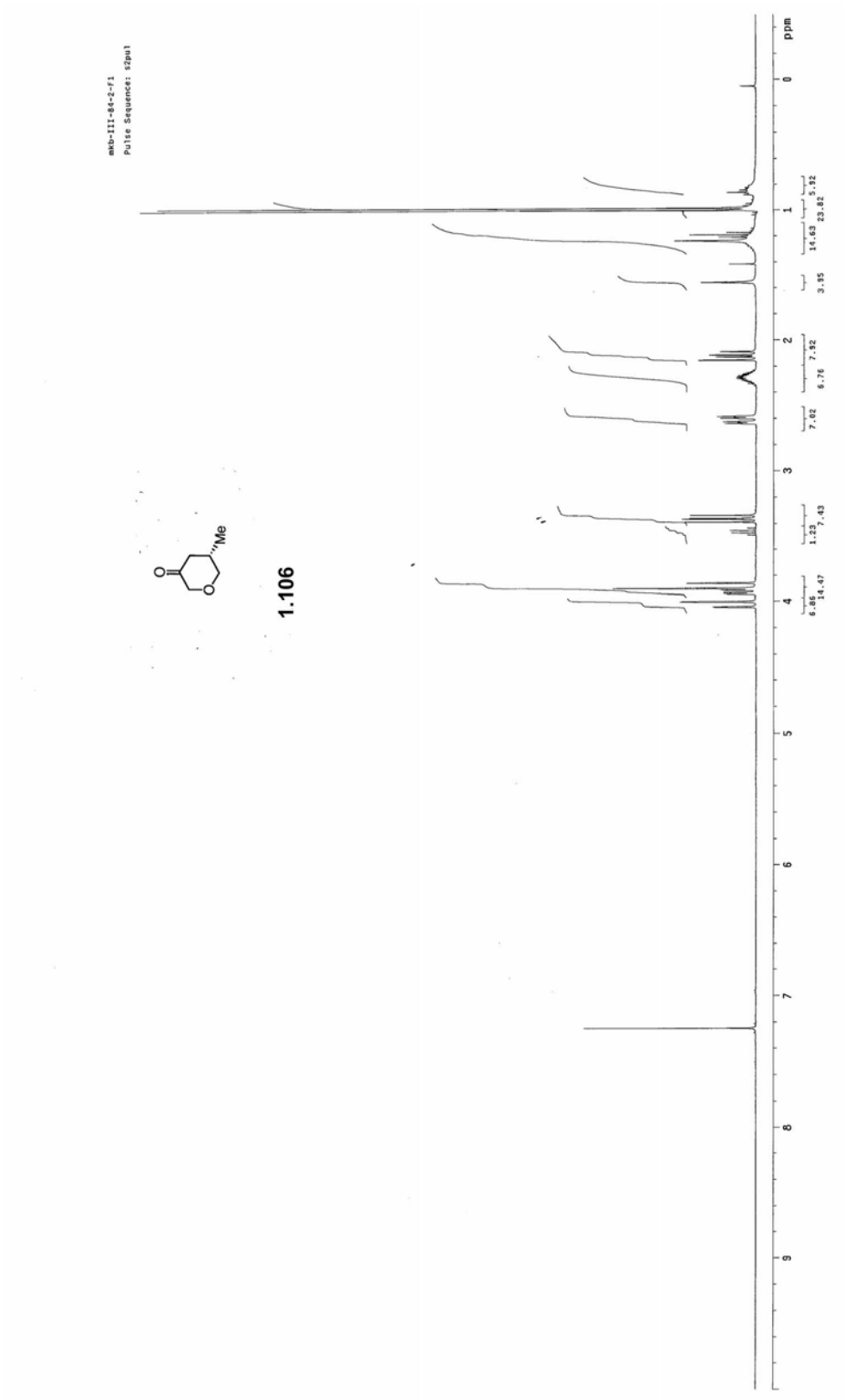
8.24
16.09
8.62
16.92
25.45

1.2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4
5
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7.92
6.76
7.02
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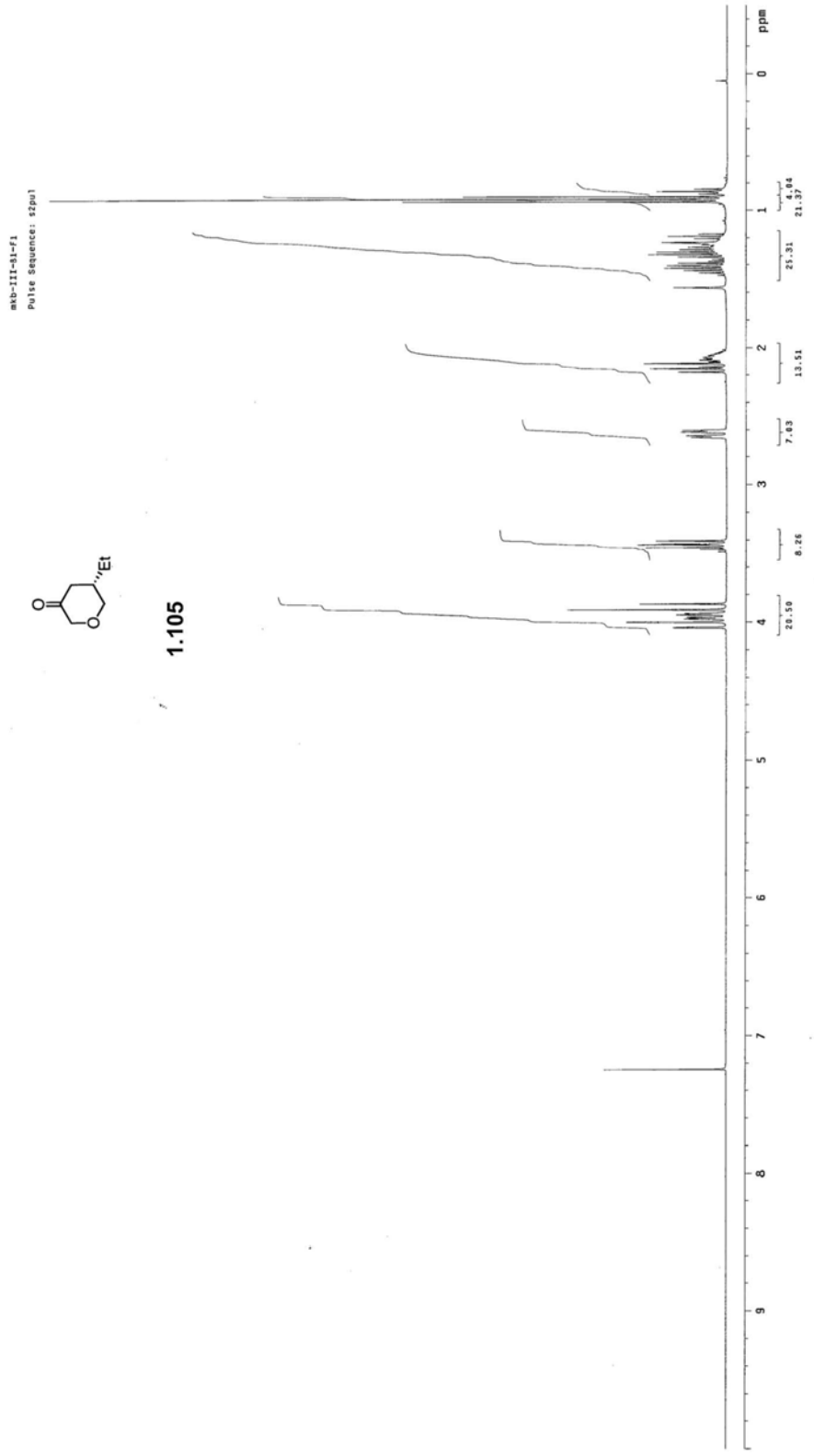
6.86
14.47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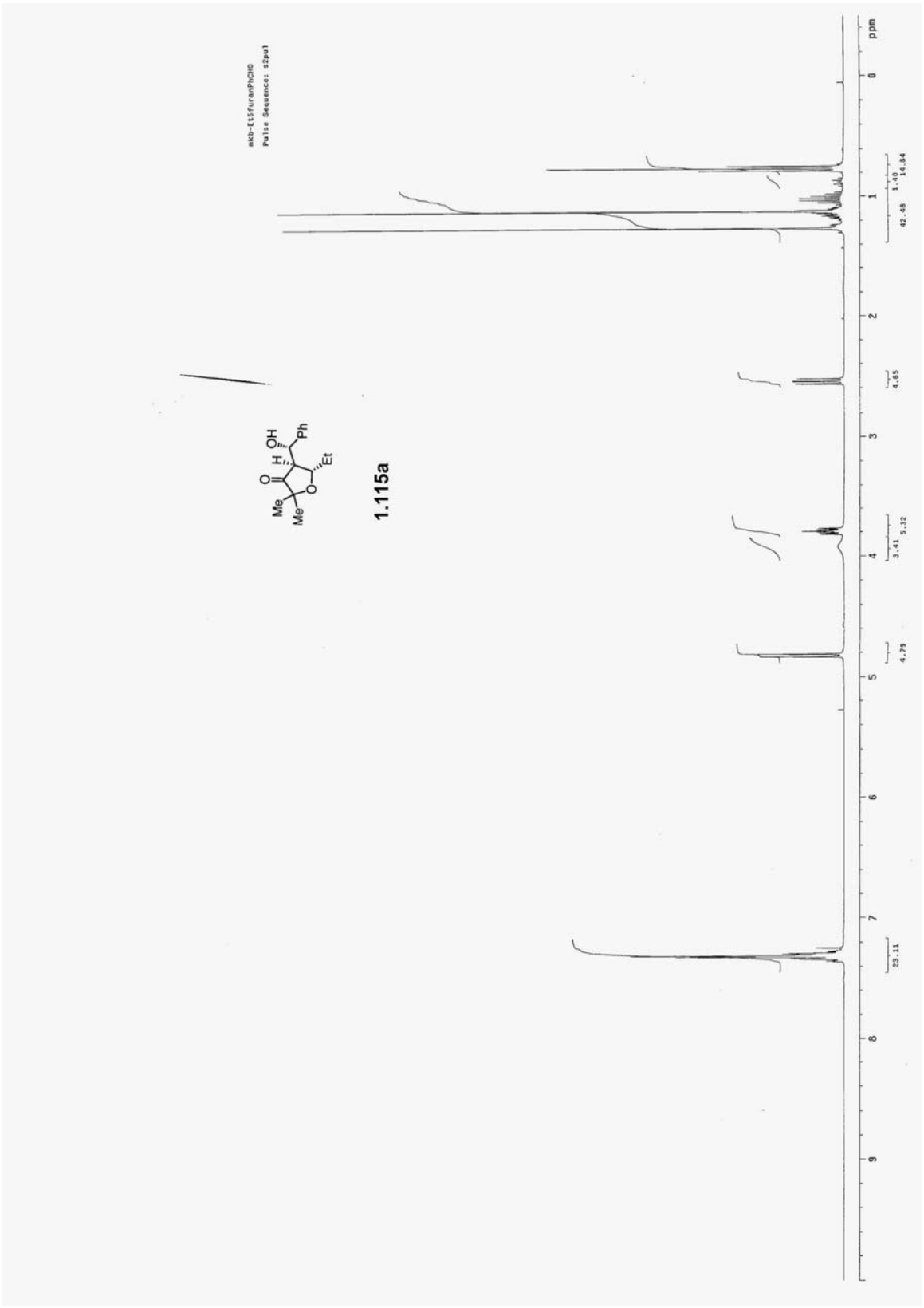
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OH
Ph
Et
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3.41
5.32
4.65
42.48
1.40
14.84

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Et
O
O
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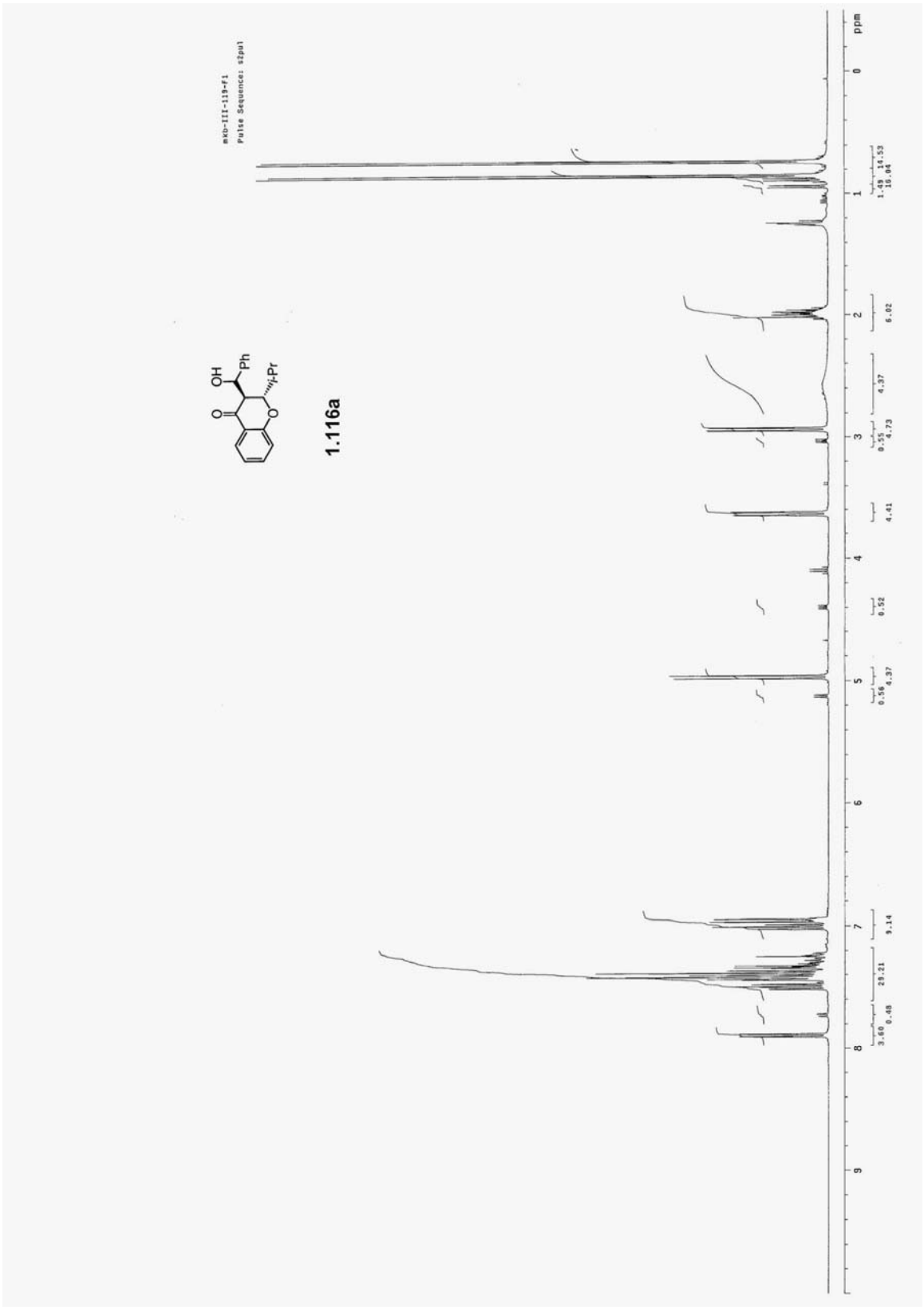
ppm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4
5
6
7
8
9
1.49
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15.04
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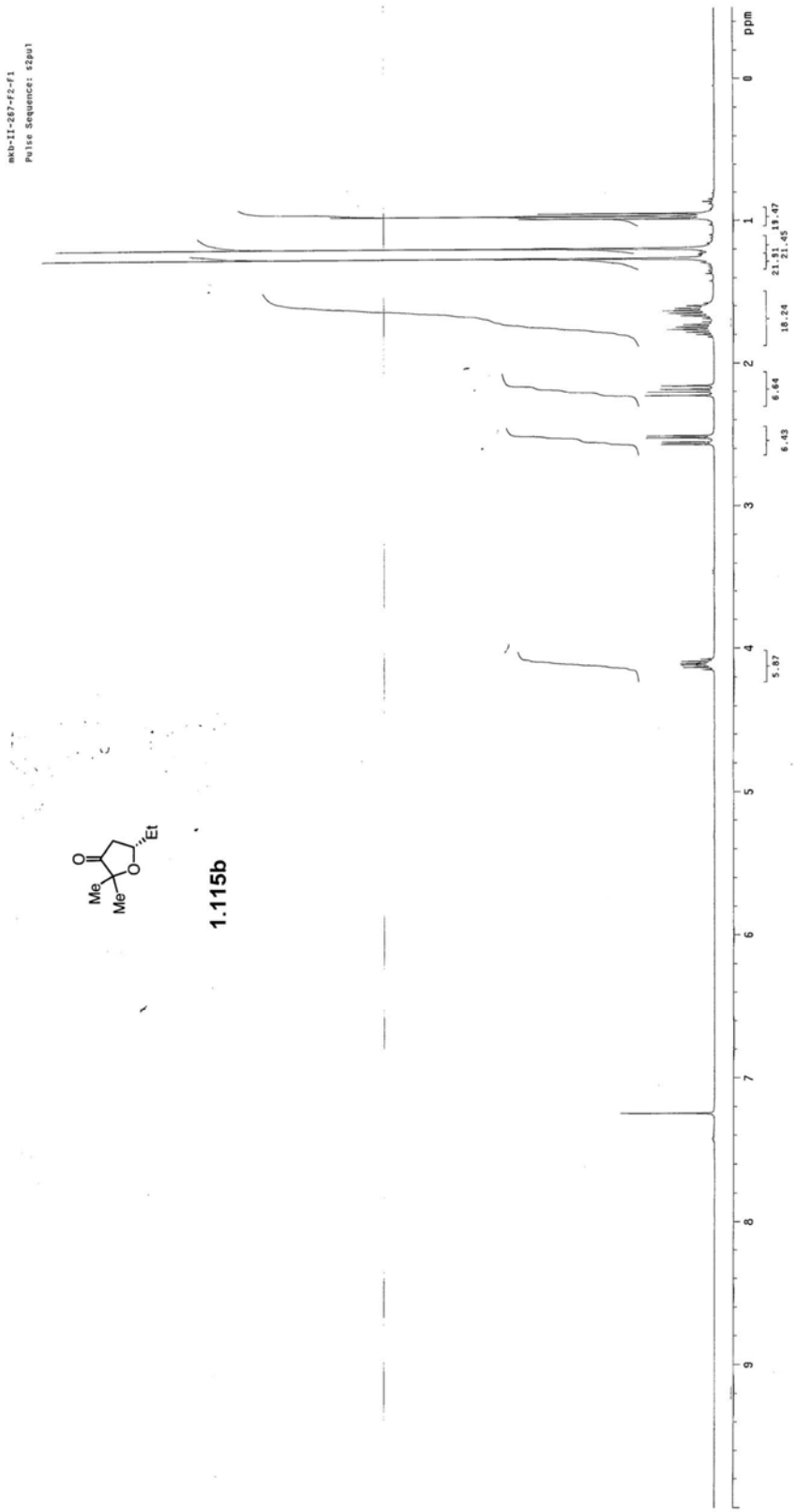
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Et
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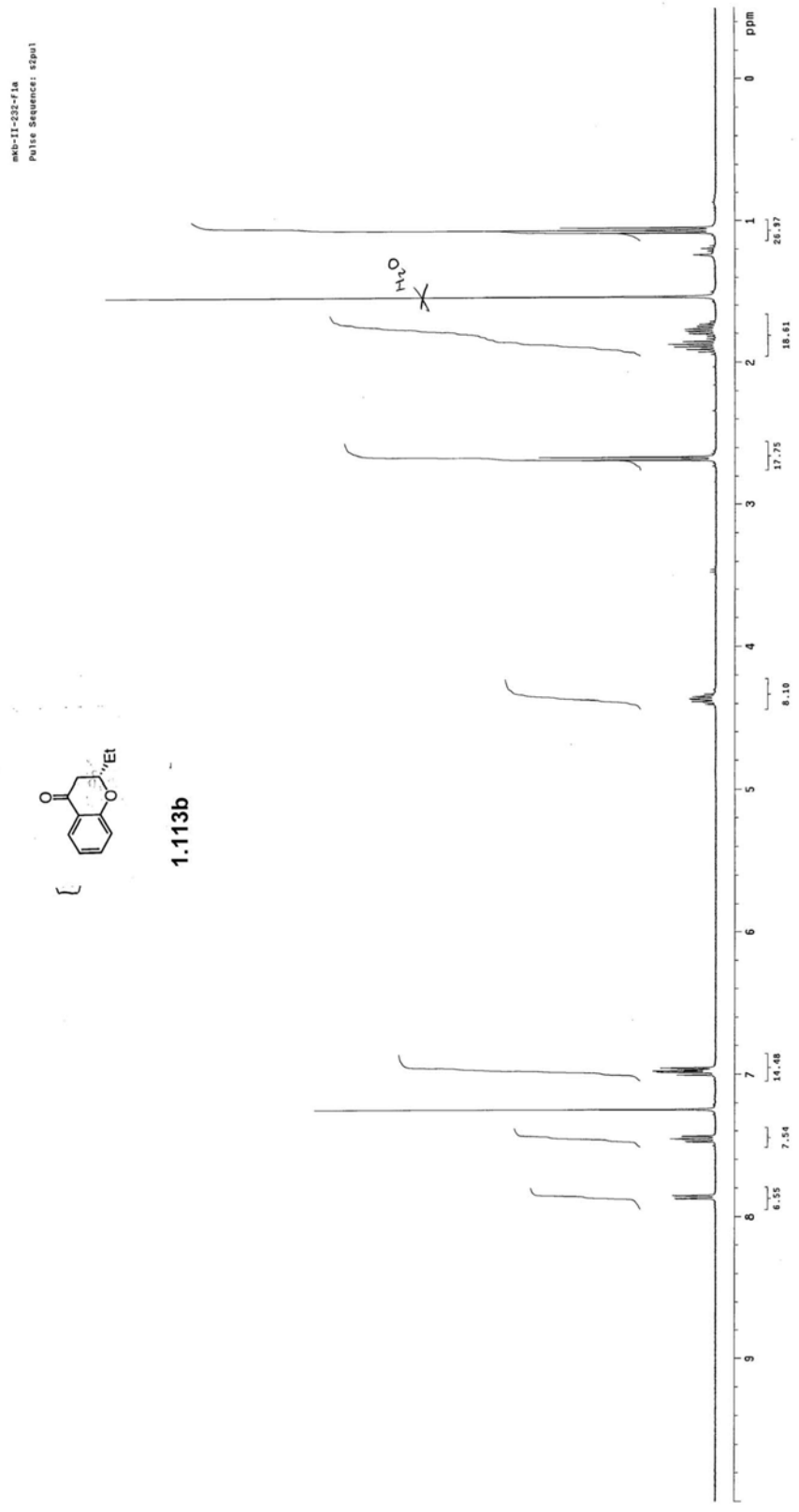
O

1.115b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7
8
9
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8.10
14.48
7.54
6.55

mxb-II-239-f1
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3
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8
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7.35
15.38
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12.23
6.40
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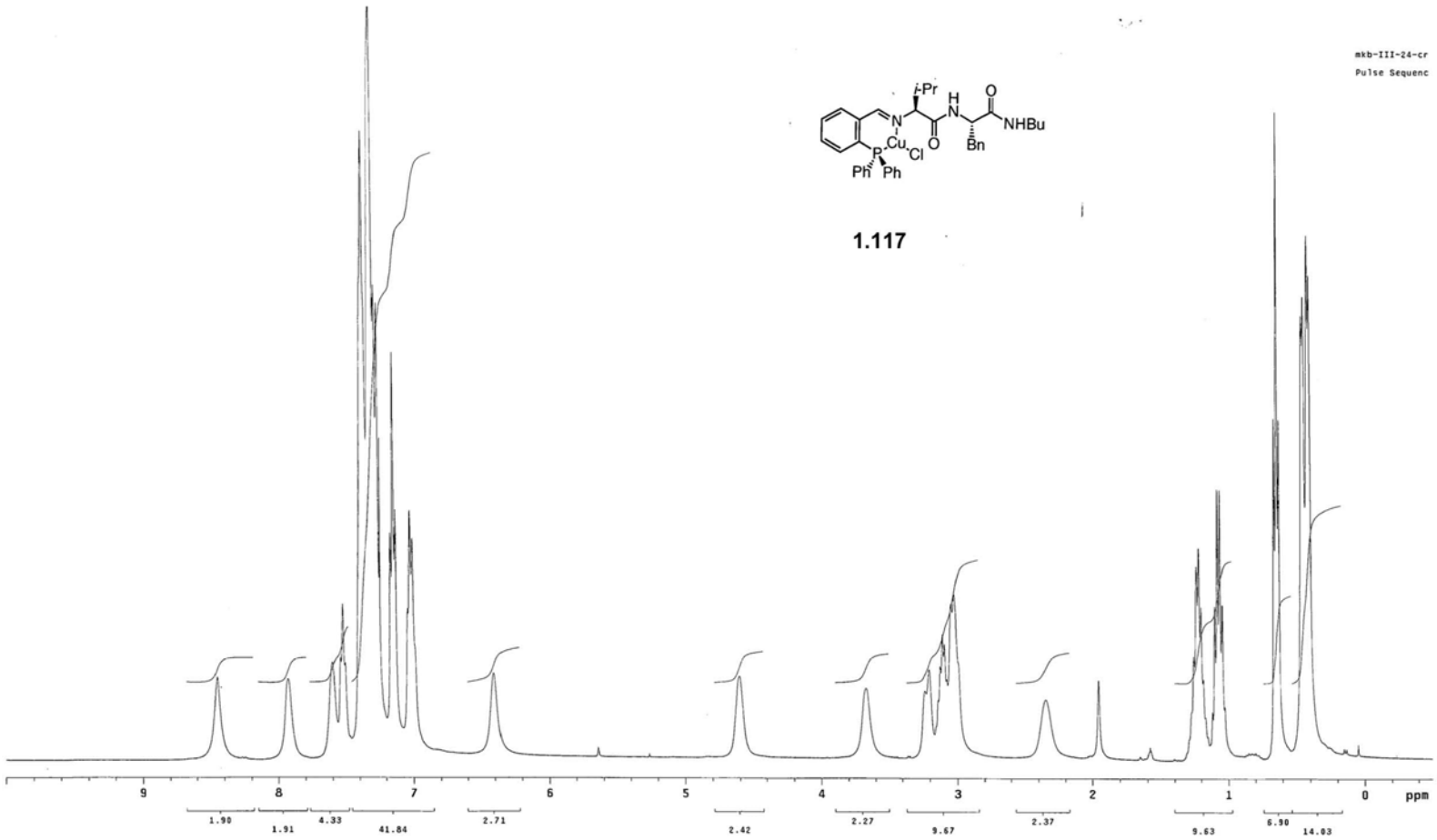
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O
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Cu
Cl
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P
Ph
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1.117
9
8
7
6
5
4
3
2
1
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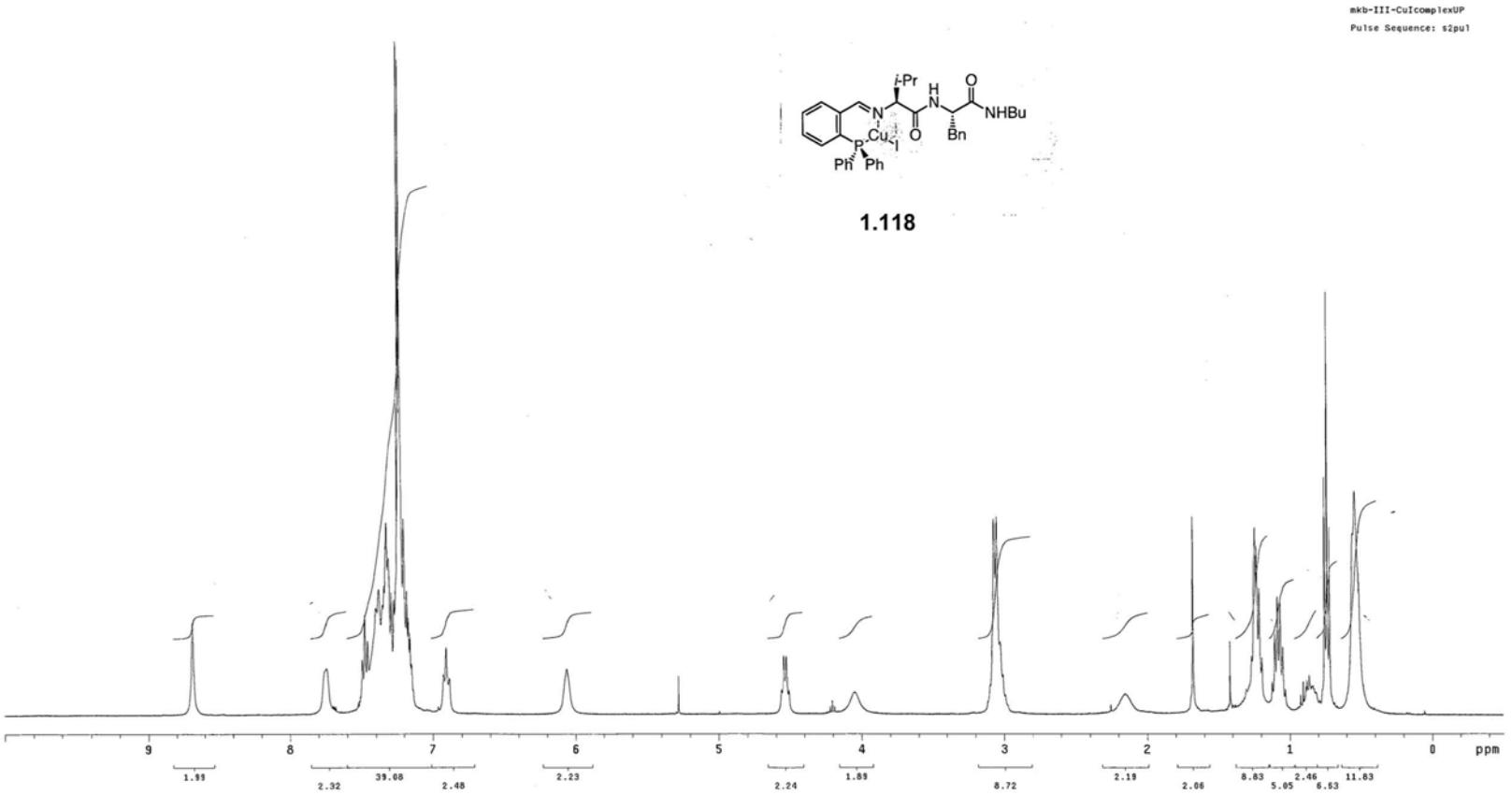
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P
Ph
Ph
9
8
7
6
5
4
3
2
1
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ppm
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2.32
39.08
2.48
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5.05
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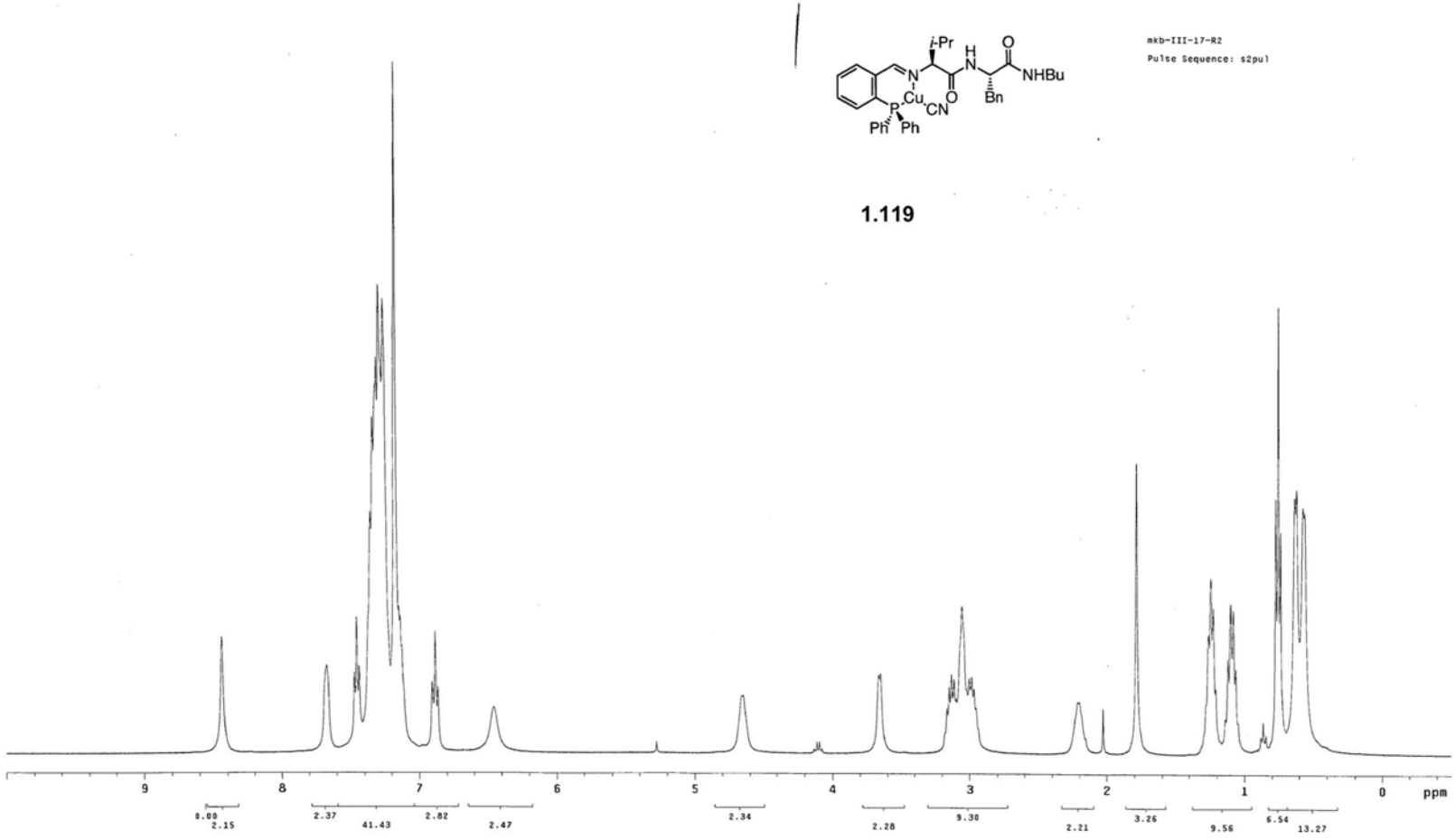
1.118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NHBu
N
Cu
CN
O
Bn
P
Ph
Ph
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9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.15
2.37
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3.26
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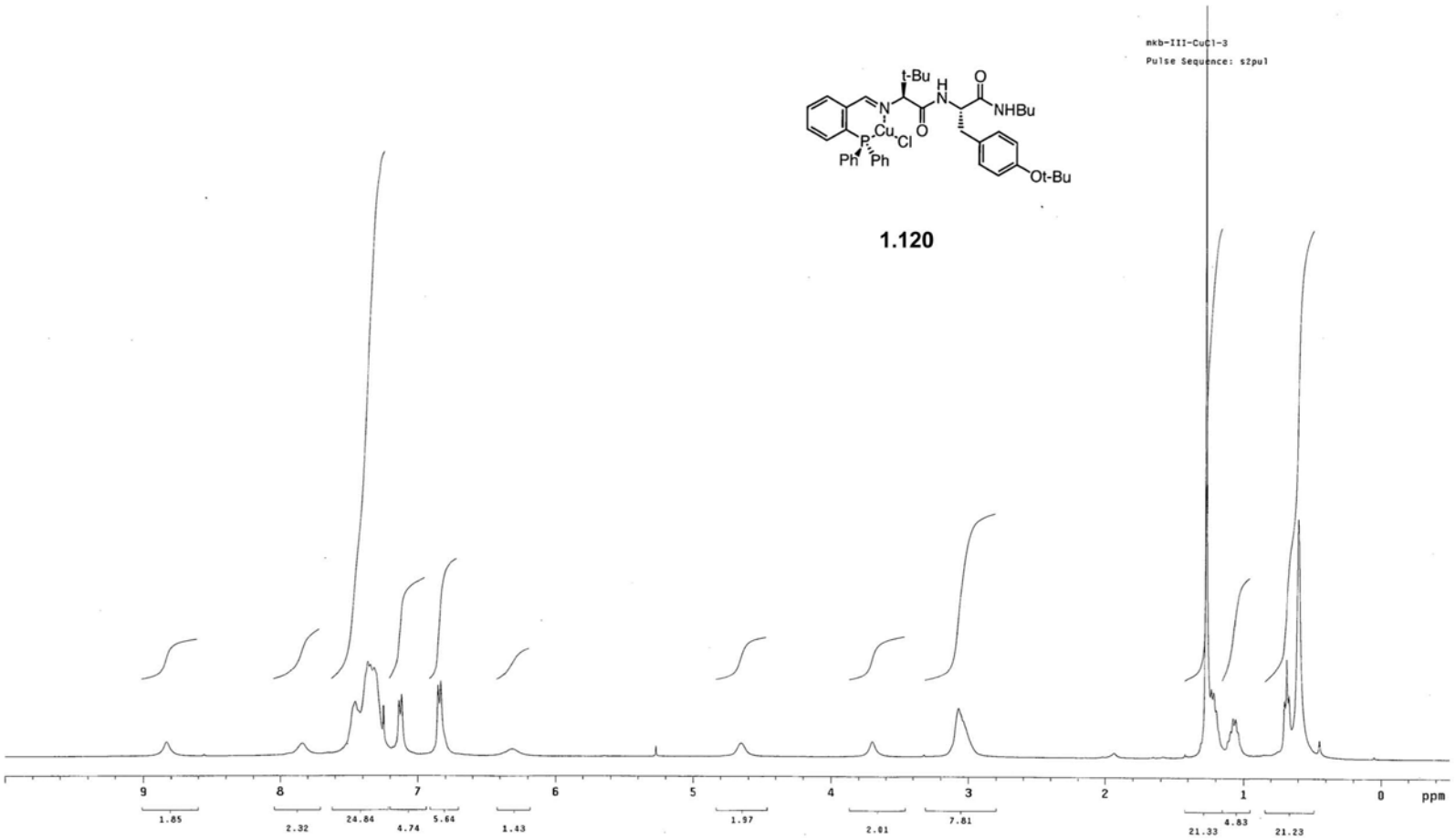
6.54
13.27

1.119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N
O
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N
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Cl
O
P
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Ph
Ot-Bu
9
8
7
6
5
4
3
2
1
0
ppm
1.85
2.32
24.84
4.74
5.64
1.43
1.97
2.01
7.81
21.33
4.83
21.23

1.120

Chapter 2. Formation of All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Addition of Diorganozinc Reagents to Unsaturated Carbonyls

2.1 *Introduction*

Catalytic enantioselective formation of all-carbon quaternary stereogenic centers has long-stood as a difficult and important problem in chemical synthesis.[55] The need to prepare all-carbon quaternary stereogenic centers stems from the presence of these motifs in natural products and biologically relevant molecules (Figure 2.1). However, relatively few methods exist for catalytic enantioselective preparation of all-carbon quaternary stereogenic centers when compared to analogous methods that deliver tertiary carbon stereogenic centers.

(55) (a) "Stereoselective Formation of Quaternary Carbon Centers and Related Functions," Denissova, I.; Barriauit, L. *Tetrahedron* **2003**, *59*, 10105-10146. (b) "Asymmetric Catalysis Special Feature Part I: Catalytic Asymmetric Synthesis of All-Carbon Quaternary Stereocenters," Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363-5367. (c) Christophers, J.; Baro A. (Eds.), *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis,* Wiley-VCH, Weinheim, **2006**.

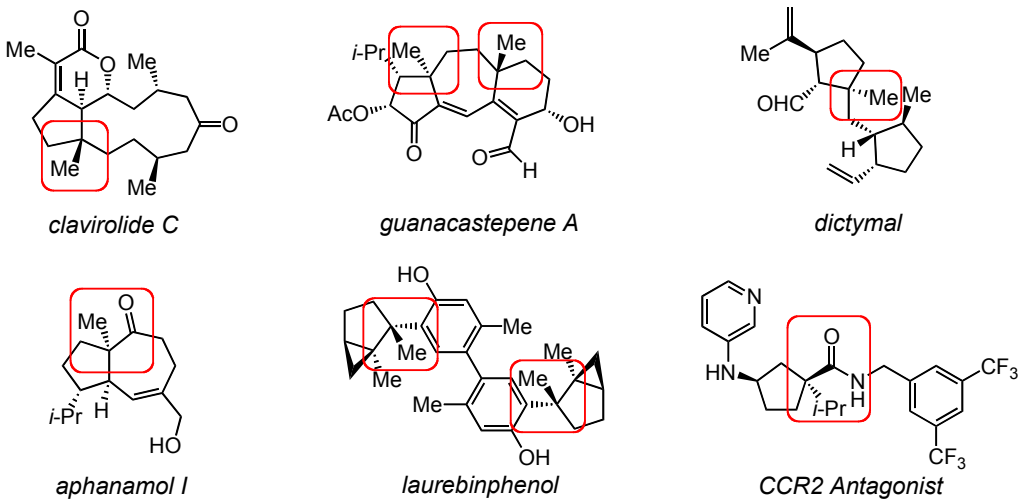

Figure 2.1: Natural Products and Medicinally Relevant Molecules Containing All-Carbon-Quaternary Stereogenic Centers

Difficulties experienced in development of methods that prepare these stereocenters generally stems from the fact that the prochiral carbon is sterically shielded towards either nucleophilic or electrophilic attack. In addition, stereo-differentiation of the prochiral carbon is more difficult as the adjacent substituents are all carbon based and thus more similarly sized (when preparing tertiary carbon stereogenic centers, one of the substituents can be a hydrogen, thus size difference is maximized). Furthermore, chiral catalysts developed for reactions that prepare tertiary carbon stereogenic centers often fail when used in the analogous transformations that deliver all-carbon quaternary stereogenic centers due to the above issues. In order to develop catalytic enantioselective methods that prepare all-carbon quaternary stereogenic centers, often new, more efficient and stereodiscriminating chiral catalysts must be discovered.

Cu-catalyzed asymmetric conjugate additions (ACAs) of organometal reagents to α, β-unsaturated carbonyls is an important class of C–C bond forming reactions.[56] Accordingly, development of this transformation has been the focus of extensive research. Processes leading to all-carbon quaternary stereogenic centers, however, have been far less studied when compared to related processes that deliver tertiary carbon stereogenic centers.[56] *This chapter will discuss our efforts aimed at developing new catalysts and methods for Cu-catalyzed ACA of diorganozinc reagents to afford quaternary all-carbon stereogenic centers.*

2.2 Background

At the time we initiated our studies (ca. 2002), no methods were reported for Cu-catalyzed enantioselective conjugate additions of organometals that delivered quaternary carbon stereogenic centers.[56] A number of reports, however, have been disclosed in the past few years, including several from our laboratories. This section will outline these disclosures.[57,58]

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(56) (a) "Recent Advances in Catalytic Enantioselective Michael Additions," Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171-196. (b) "Enantioselective Copper-Catalyzed Conjugate Addition," Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221-3236. (c) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. in *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, pp. 224-258. (d) "Recent Advances in Metal-Catalyzed Asymmetric Conjugate Additions," Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279-1300. (e) "Enantioselective Copper-Catalyzed Conjugate Addition and Allylic Substitution Reactions," Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pámies, O.; Diéguez, M. *Chem. Rev. ASAP*.

(57) "Formation of All-Carbon Quaternary Centers by Copper-Catalyzed Asymmetric Conjugate Addition," Alexakis, A.; Vuagnoux-d'Augustin, M.; Martin, D.; Kehrli, S.; Palasi, L.; Hénon, H.; Hawner, C. *Chima*, **2008**, *62*, 461-464.

(58) For Rh-catalyzed addition of alkenyl- and arylboronic acids to afford all-carbon quaternary stereogenic centers, see: (a) "Enantioselective Construction of Stereogenic Quaternary Centres *via* Rh-Catalyzed Asymmetric Addition of Alkenylboronic Acids to α,β-Unsaturated Pyridylsulfones," Mauleón, P.; Carretero, J. C. *Chem. Commun*, **2005**, 4961-4693. (b) "Rhodium-Catalyzed Asymmetric Construction of

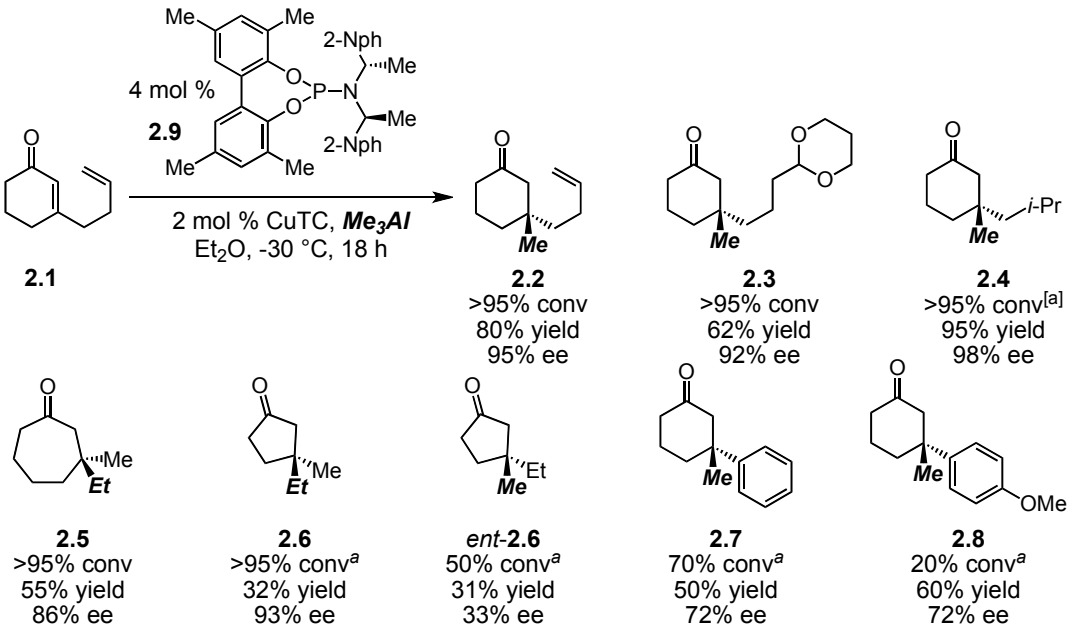
In 2005, Alexakis and coworkers disclosed the first example for Cu-catalyzed ACA of alkylmetal reagents to β-substituted cyclic enones (Scheme 2.1).[59] Highly enantioselective (>90% ee) additions of trialkylaluminum reagents to β-substituted cyclohexenone derivatives (i.e. **2.1**) were efficiently promoted by 4.0 mol % chiral phosphoramidite **2.9** and 2.0 mol % CuTC. The system is sensitive to sterically bulky substituents surrounding the enone as represented by the higher catalyst loadings (8.0 vs. 4.0 mol %) and more reactive (and more sensitive) Cu-source ($(CuOTf)_2 \bullet C_6H_6$ vs. CuTC) required to acheive efficient addition with β-isobutyl-derived substrates (formation of **2.4**). Furthermore, only additions of Me_3Al and Et_3Al were disclosed. In subsequent reports, the substrate scope was expanded to include β-substituted cyclopentenone and cycloheptenone substrates.[60] While good enantioselectivity (>85% ee) was realized for additions of Et_3Al, yields of isolated products **2.5** and **2.6** were low (<60% yield). Furthermore, additions of Me_3Al to either β-ethyl-cyclopentenone **(**preparation of *ent*-**2.6**) or β-aryl-substituted cyclohexenones **(**synthesis of **2.7** and **2.8**) were inefficient (<70% conv) and resulted in moderate to low enantioselectivities (<75% ee).

Quaternary Carbon Stereocenters: Ligand-Dependent Regiocontrol in the 1,4-Addition to Substituted Maleimides," Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628-5629.

(59) "Enantioselective Copper-Catalyzed Conjugate Addition to Trisubstituted Cyclohexenones: Construction of Stereogenic Quaternary Centers," d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376-1378.

(60) "Copper-Catalyzed Asymmetric Conjugate Addition of Trialkylaluminium Reagents to Trisubstituted Enones: Construction of Chiral Quaternary Centers," Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem. Eur. J.* **2007**, *13*, 9647-9662.

Scheme 2.1: ACA of Trialkylaluminium Reagents Disclosed by Alexakis and Co-workers

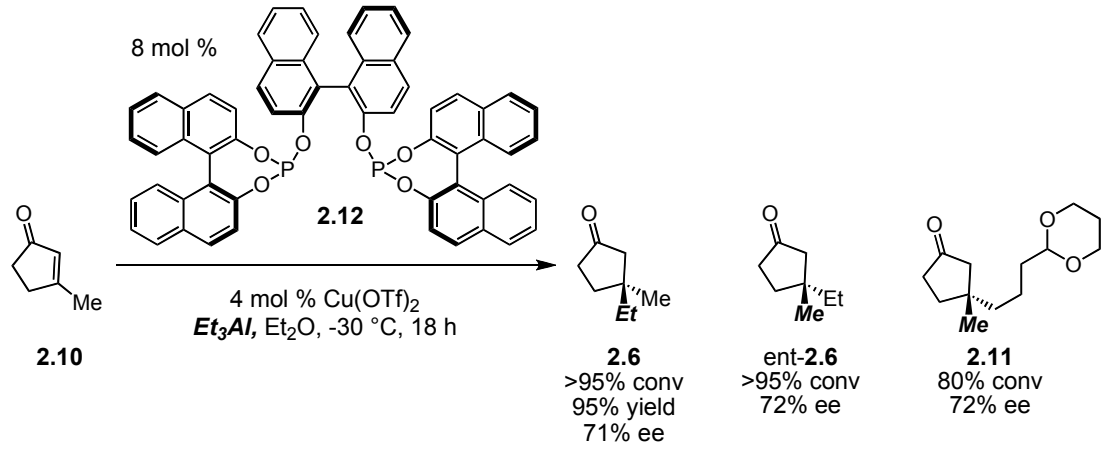


[a] Reactions carried out with 8 mol % catalyst, $(CuOTf)_2 \bullet C_6H_6$ as the Cu source.

Alexakis and coworkers later discovered that phosphite-based ligand **2.12** could promote the addition of trimethyl- and triethylaluminium reagents to β-substituted cyclopentenones derivatives with moderate enantioselectivities (71-72% ee) and provide the desired products (**2.6** and **2.11**) in high efficiency (80-95% conv, yield reported in a single example, Scheme 2.2).[61] For substrates bearing larger β-substituents, efficiencies began to suffer (80% conv) while enantioselectivities remained moderate (72% ee) **(**formation of **2.11**).

(61) "Enantioselective Copper-Catalyzed Conjugate Addition to 2- or 3-Substituted Cyclopent-2-en-1-ones: Construction of Stereogenic Quaternary Carbon Centers," Vuagnoux-d'Augustin, M.; Kehrli, S.; Alexakis, A. *Synlett*, **2007**, *13*, 2057-2060.

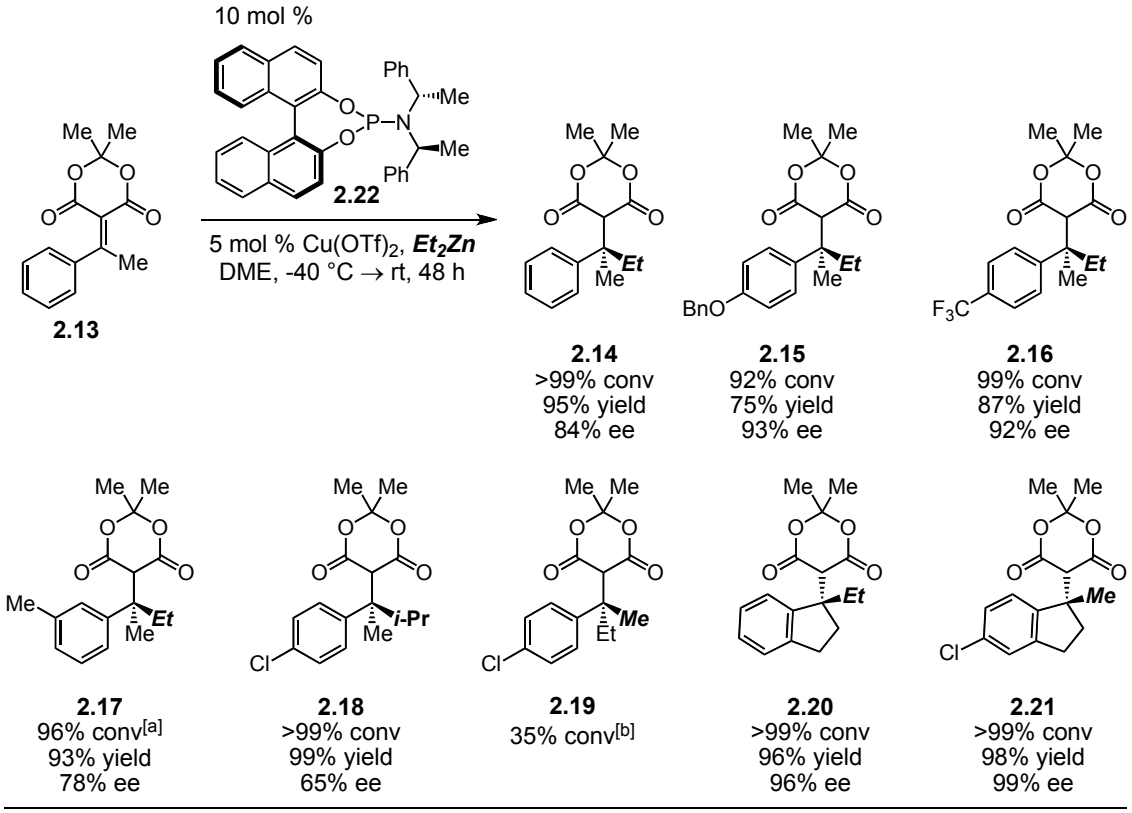
Scheme 2.2: Enantioselective Additions to β-Alkyl Cyclopentenones



Phosphoramidite-based ligands have also found utility for enantioselective Cu-catalyzed conjugate additions of dialkylzinc reagents to arylalkylidene Meldrum's acid-based substrates (i.e., **2.13**), as reported by Fillion and coworkers.[62] As illustrated in Scheme 2.3, highly enantioselective ACA of Et_2Zn were carried out to a variety enones bearing electronically modified aryl groups (**2.15** and **2.16**). Additions to sterically modified systems, however, have been met with limited success. *Meta*-substituted aryl rings are tolerated, albeit relatively lower enantioselectivity was observed (78% ee for **2.17**), while substrates containing *ortho*-substituted aryl groups led to inefficient reactions (<2% conv, not shown). Reactions with *i*-Pr_2Zn were efficient, but less selective (>99% conv and 65% ee for **2.18**), while additions of Me_2Zn results in low conversions (35% conv for **2.19**). Finally, indane based substrates performed well with this system for both the addition of Et_2Zn and Me_2Zn; the desired products (**2.20**-**2.21**) were obtained in high enantioselectivities (>96% ee) and yields (>96%).

(62) "Asymmetric Synthesis of All-Carbon Benzylic Quaternary Stereocenters via Cu-Catalyzed Conjugate Addition of Dialkylzinc Reagents to 5-(10-Arylalkylidene) Meldrum's Acids," Fillion, E.; Wilsily, A. *J. Am. Chem. Soc.* **2006**, *128*, 2774-2775.

Scheme 2.3: Enantioselective Conjugate Addition to Arylalkylidene Meldrum's Acids



[a] Reaction time = 72 h. [b] Enantioselectivity and yield not determined.

In an extension of the original method, Fillion and coworkers have reported highly enantioselective additions of dialkylzinc reagents to Meldrum's acid-based substrates that bear an ester substituent (i.e., **2.23**, Scheme 2.4).[63] In these examples, Cu-catalyzed ACAs to methyl, *t*-butyl as well as thioester-derived substrates delivered products **2.24**-**2.26** in good yields (>90%) and with high selectivities (>86% ee). Additions of *i*-Pr_2Zn and Me_2Zn (synthesis of **2.28** and **2.29**, respectively) could be carried out with high efficiency; however, enantioselectivity was low in the latter case

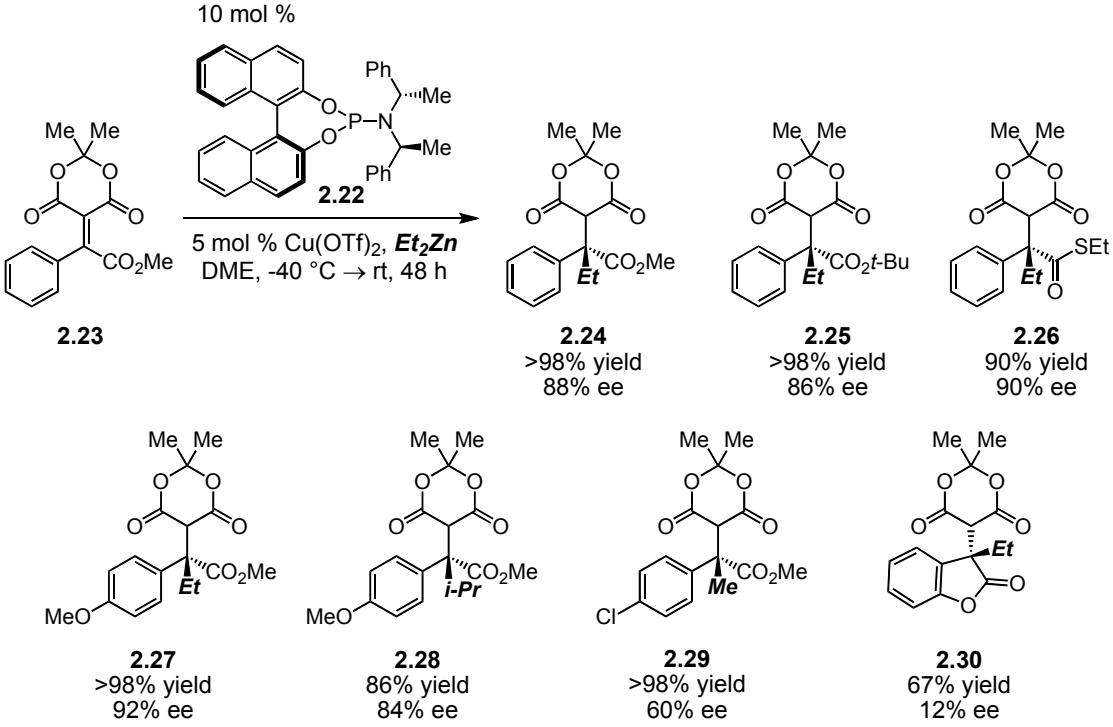
(63) "Asymmetric Synthesis of Carboxylic Acid Derivatives Having an All-Carbon α-Quaternary Center through Cu-Catalyzed 1,4-Addition of Dialkylzinc Reagents to 2-Aryl Acetate Derivatives," Wilsily, A.; Fillion, E. *Org. Lett*. **2008**, *10*, 2801-2804.

(60% ee). Finally, additions to lactone-derived substrates, while efficient, were non-selective (formation of **2.30**). In a separate disclosure, moderately enantioselective (65% ee) 1,6-additions of Et_2Zn could be carried out with propenylidene substituted Meldrum's acid **2.31** (Scheme 2.4).[64] This reaction represents the first example of a 1,6-addition to furnish an all-carbon quaternary stereogenic center though ACA.

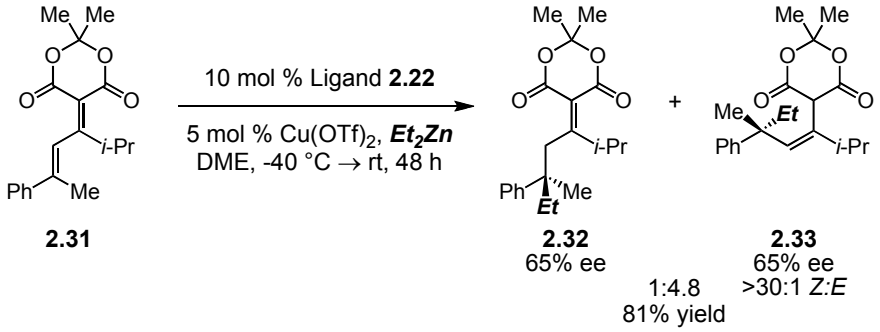
(64) "Asymmetric Cu-Catalyzed 1,6-Conjugate Addition of Dialkylzinc Reagents to 5-(3-Aryl-2-Propenylidene) Meldrum's Acids," Fillion, E.; Wilsily, A.; Liao, E-T. *Tetrahedron: Asymmetry* **2006**, *17*, 2957-2959.

Scheme 2.4: Cu-Catalyzed ACA to Meldrum's Acid Derivatives

■ *Aryl Acetate-Derived Meldrum's Acids*



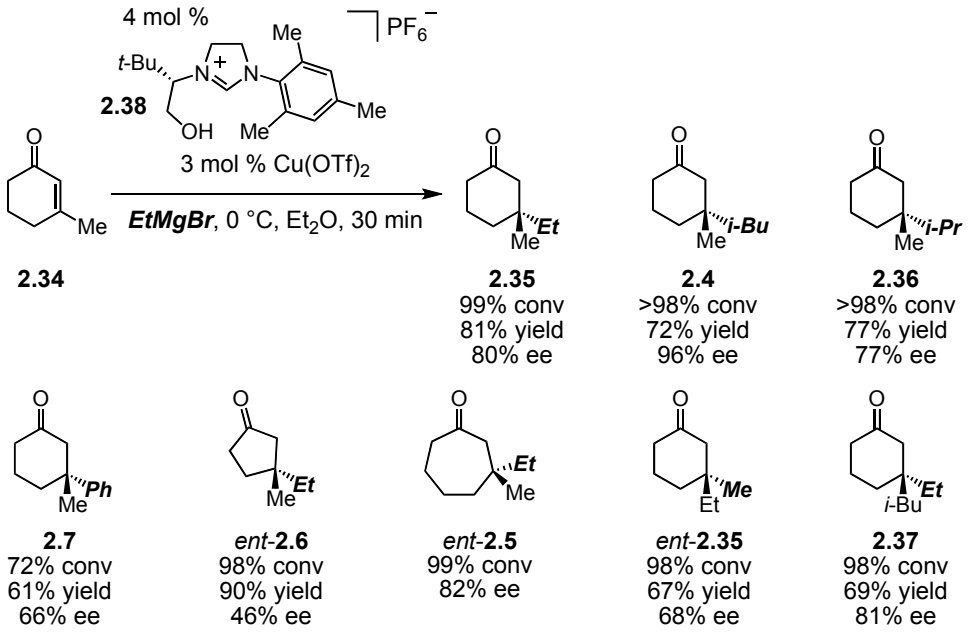
■ *Propenylidene-Derived Meldrum's Acids*



In 2006, Mauduit and Alexakis disclosed a practical and efficient method for Cu-catalyzed ACA of Grignard reagents to unactivated cyclic enones (i.e., **2.34**) promoted by

a chiral *N*-heterocyclic carbene (NHC) precursor **2.38**.[65] Several points regarding this method are noteworthy. (1) In all cases, <2% 1,2-addition was observed. (2) Slow addition of the Grignard reagent over 30 min was necessary to obtain optimal selectivities. If the Grignard reagent was added prior to addition of the substrate, <2% ee was observed. (3) While high enantioselectivities (>90%) were observed in select cases (i.e., synthesis of **2.4**) the majority of the examples were <85% ee (**2.35**-**2.37**). (4) Additions to cyclopentenone derivatives were significantly less selective (*ent*-**2.6** was generated in 42% ee).

Scheme 2.5: Cu-Catalyzed ACA of Grignard Reagents: Mauduit and Alexakis

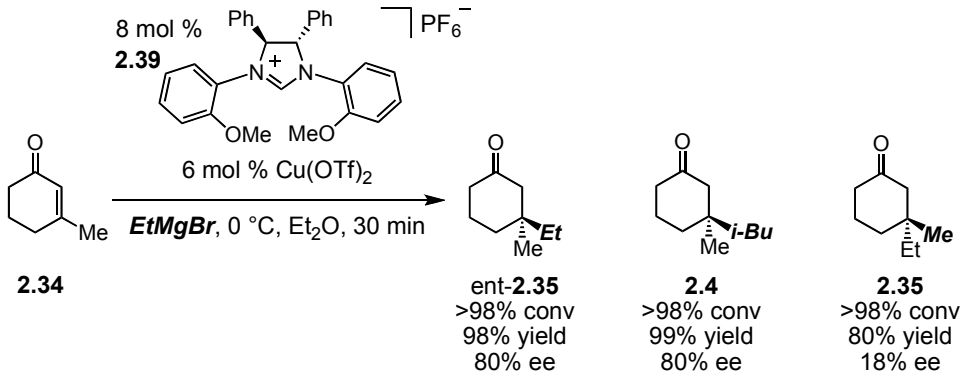


Related to studies reported by Mauduit and Alexakis,[65] Tomioka has developed a new monodentate NHC (**2.39**) for Cu-catalyzed ACA of Grignard reagents (Scheme

(65) "Copper-Catalyzed Asymmetric Conjugate Addition of Grignard Reagents to Trisubstituted Enones. Construction of All-Carbon Quaternary Chiral Centers," Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416-8417.

2.6).[66] The *ortho*-methoxy aryl units were required to achieve optimal levels of enantioselectivity (~80% ee). Reactions with chiral NHC complexes where the OMe moiety was replace with either H- or Me- led to formation of ent-**2.35** in 60% ee. Long alkyl chain Grignard reagents were suitable nucleophiles for this process; ketone **2.4** was delivered with good enantioselectivity (>75% ee). However, use of PhMgBr or MeMgBr provided the products (i.e., **2.35**) in low ee (<34% ee).

Scheme 2.6: Cu-Catalyzed ACA of Grignard Reagents: Tomioka



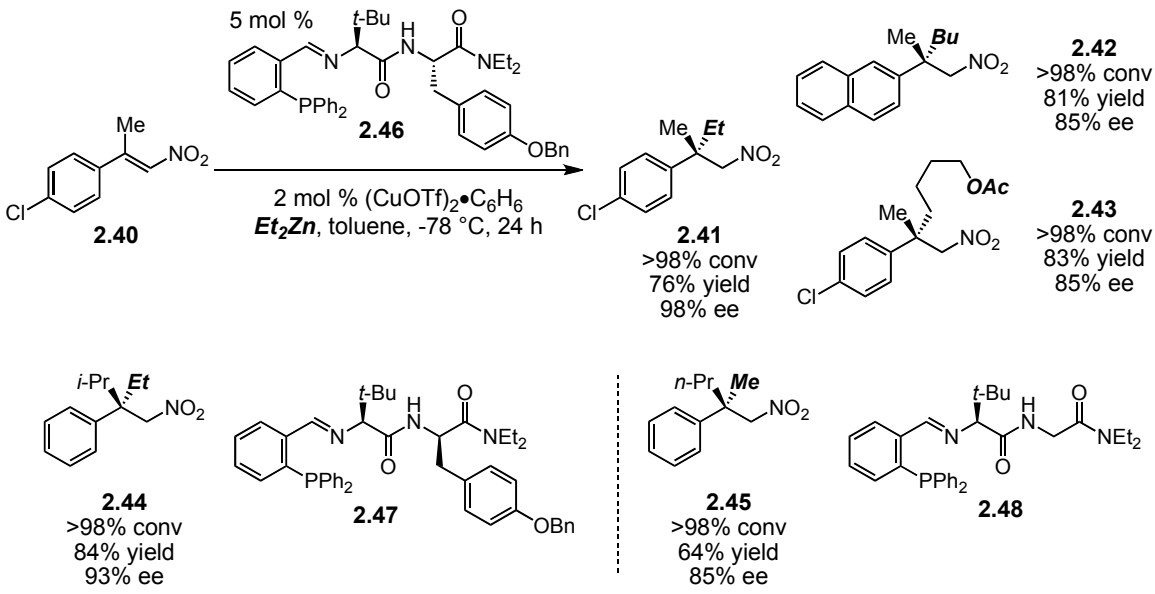
In our laboratories, we have disclosed several methods for Cu-catalyzed ACAs to prepare all-carbon quaternary stereogenic centers. All of these methods utilized peptide-based ligands developed in our laboratories (see Chapter 1 for examples and a discussion about this class of ligands).[67]

(66) "C_2 Symmetric Chiral NHC Ligand for Asymmetric Quaternary Carbon Constructing Copper-Catalyzed Conjugate Addition of Grignard Reagents to 3-Substituted Cyclohexenones," Matsumoto, Y.; Yamada, K.-i.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578-4581.
(67) "Small Peptides as Ligands for Catalytic Asymmetric Alkylations of Olefins. Rational Design of Catalysts or of Searches that Lead to Them?," Hoveyda, A. H.; Hird. A. W.; Kacprzynski, M. A. *Chem. Commun*, **2004**, 1779-1785.

The first report from our group detailed Cu-catalyzed ACA of dialkylzinc reagents to trisubstituted nitroalkenes (i.e., **2.40**, Scheme 2.7).[68] Reactions were carried out in the presence of 5.0 mol % peptide-based ligand **2.46** in combination with 2.0 mol % $(CuOTf)_2 \bullet C_6H_6$. Highly enantioselective (85-98% ee) and efficient additions of Et_2Zn, Bu_2Zn as well as an acetate-containing dialkylzinc reagent to β-aryl-β-methyl nitroalkenes were carried out. For nitroalkenes bearing slightly larger β-substituents (*i*-Pr or *n*-Pr vs. Me) modified ligands **2.47**-**2.48** were required, as reactions to prepare these products (**2.44** and **2.45**) were less enantioselective with chiral ligand **2.46** (for example, **2.44** was generated in >98% conv, 53% yield, 79% ee). Reactions to prepare nitroalkane products **2.41**-**2.43** with modified ligands **2.47**-**2.48** were less efficient and selective. For example, conjugate addition of Et_2Zn promoted by **2.47** or **2.48** provided **2.41** in 89% ee (>98% conv) or 66% ee (13% conv), respectively.

(68) "Enantioselective Synthesis of Nitroalkanes Bearing All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Additions," Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584-4585.

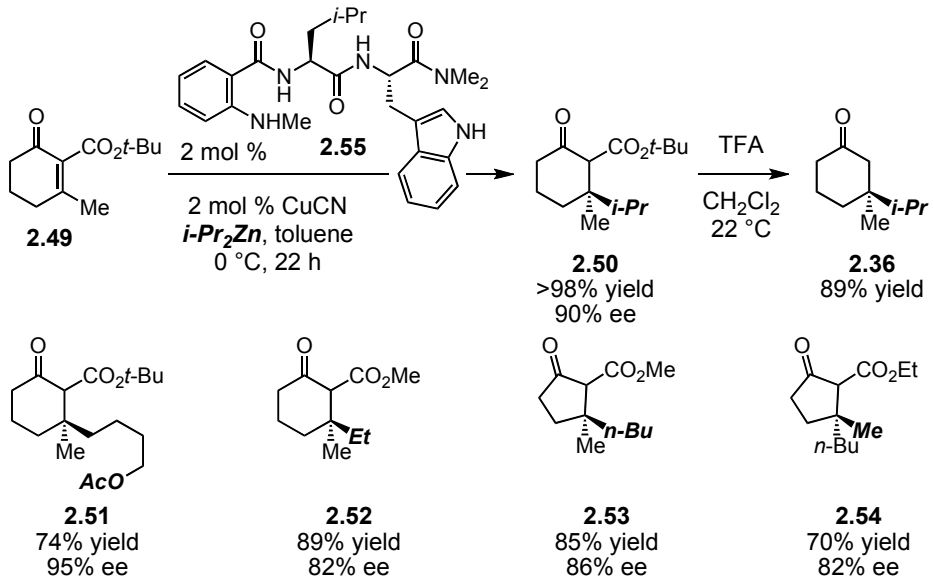
Scheme 2.7: ACA of Dialkylzinc Reagents to Trisubstituted Nitroalkenes



In 2005, we disclosed a method for highly enantioselective conjugate additions to tetrasubstituted cyclic enones (i.e., **2.49**, Scheme 2.8).[69] Additions were efficiently promoted by chiral peptide-based ligand **2.55** in combination with CuCN and could be carried out with a variety of dialkylzinc reagents to both five- and six-membered ring substrates. Substrates bearing a larger ester substituent (*t*-Bu vs. Me) led to slightly more enantioselective processes. Additions to five-membered ring substrates, however, were less selective than six-membered ring substrates (compare **2.50**-**2.52** and **2.53**-**2.54**). The ester substituent was efficiently removed through treatment of the β-ketoester with TFA to provide the cyclic ketone **2.36** in 89% yield.

(69) "Catalytic Enantioselective Alkylations of Tetrasubstituted Olefins. Synthesis of All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Enones," Hird. A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988-14989.

Scheme 2.8: Cu-Catalyzed ACA to Tetrasubstituted Enones



2.3 *ACA to Cyclic Unsaturated γ-Ketoesters Promoted by Peptide-Based Ligands*

At the time we initiated our studies, the only methods disclosed for ACA to furnish all-carbon quaternary stereogenic centers are illustrated in Schemes 2.1, 2.7-2.8. While each of these methods represents a substantial contribution to the field of ACA (as well as synthetic organic chemistry), the products lacked a readily functionalizable group α- to the all-carbon quaternary stereogenic center. It was the goal of the following studies to develop a method for ACA to cyclic unsaturated γ-ketoesters (i.e., **2.56**, Figure 2.2), as additions to this class of enones would provide products readily amenable to functionalization. Potential applications of this method are illustrated in Figure 2.2.

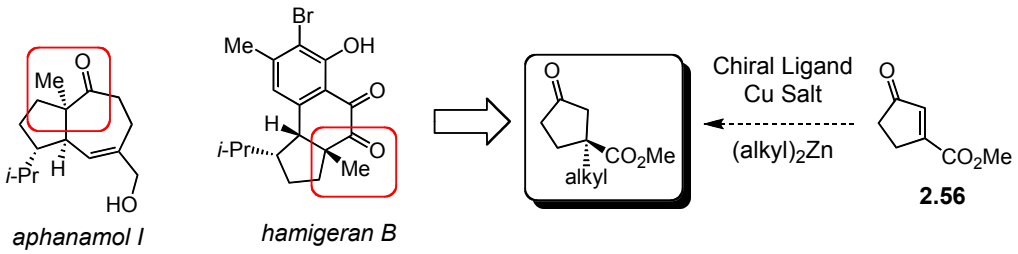
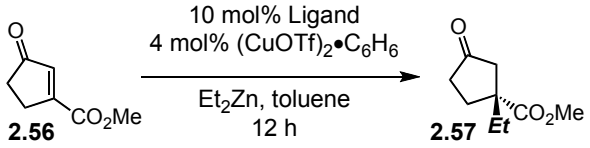


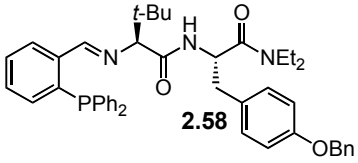
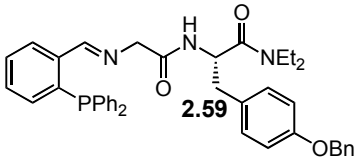
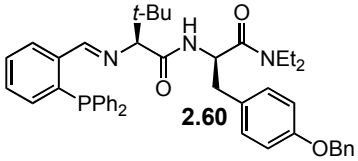
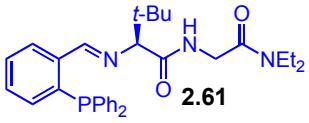
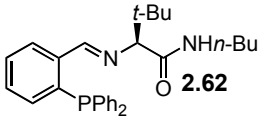
Figure 2.2: Natural Product that may be Accessed Through ACA to Cyclic Unsaturated γ-Ketoesters

In our initial investigations, we examined the ability of peptide-based phosphine ligands, developed in these laboratories for highly efficient and enantioselective Cu-catalyzed ACA to various unsaturated carbonyls (see Chapter 1), to promote the addition of Et_2Zn to γ-ketoester **2.56**.[67] Initial results were encouraging as we discovered that 10 mol % chiral ligand **2.58** in combination with 4 mol % $(CuOTf)_2 \bullet C_6H_6$ provided **2.57** efficiently (>98% conv, 12 h) and with moderate selectivity (55% ee) (Table 2.1, entry 1). To gain insight into the importance of each portion of the modular peptide-based ligand we prepared ligands **2.59**-**2.62**. When diastereomer **2.60** was utilized, increased selectivity was observed (82% ee vs. 55% ee at 4 °C, Table 2.1, entries 1 and 3). In addition, when glycine-containing ligand **2.61** was used, equally high levels of selectivity were obtained (80% ee, at 4 °C, Table 2.1, entry 5). It is important to note that the presence of an AA2 moiety was crucial for selectivity. When mono-amino acid based ligand **2.62** was employed, **2.57** was obtained in only 34% ee. Further optimization revealed that lower reaction temperature (-30 °C) led to an increase in enantioselectivity (88-89% ee, Table 2.1, entries 5-6) while efficiency remained high (>98% conv, 12 h). Though glycine containing ligand **2.61** afforded **2.57** with slightly lower levels of

selectivity than **2.60** (89% ee vs. 88% ee), we chose chiral ligand **2.61** to use in further optimization studies due to its simplicity.

Table 2.1: Initial Screening of Various Chiral Peptide Based Ligands



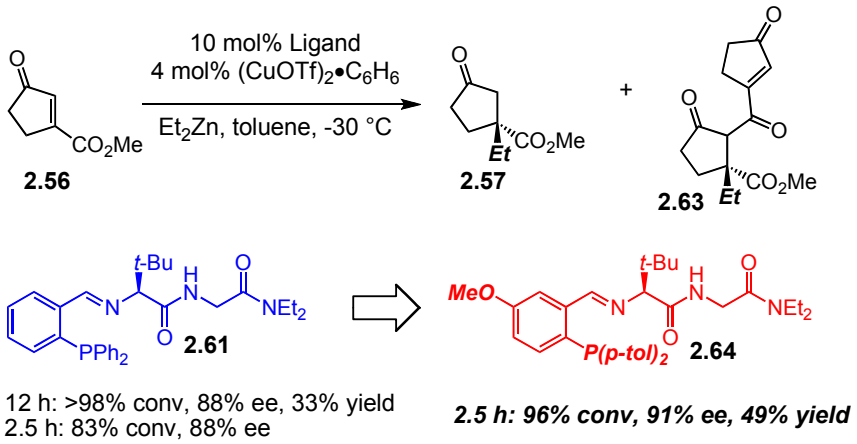
entry	Ligand	temp (°C)	conv (%)[a]	ee (%)[a]
1	 **2.58**	0	98	55
2	 **2.59**	0	98	-26
3	 **2.60**	0	98	82
4		-30	>98	***89***
5	 **2.61**	0	98	80
6		-30	98	***88***
7	 **2.62**	0	98	34
8				

[a] Determined by chiral GLC analysis

Though ACA promoted by **2.61** proceeded to >98% conversion and with good selectivity (88% ee), the isolated yields were low (33%) due to Clasien condensation of the generated zinc enolate with **2.56** to provide **2.63** (Scheme 2.9). We proposed that a

more electron rich Cu(I)-alkyl species might increase the rate of the ACA reaction, thus reducing the occurrence of byproduct formation. Accordingly, synthesis and application of several electron rich phosphine Schiff bases led us to discover ligand **2.64** as a more efficient ligand (49% yield, 91% ee).

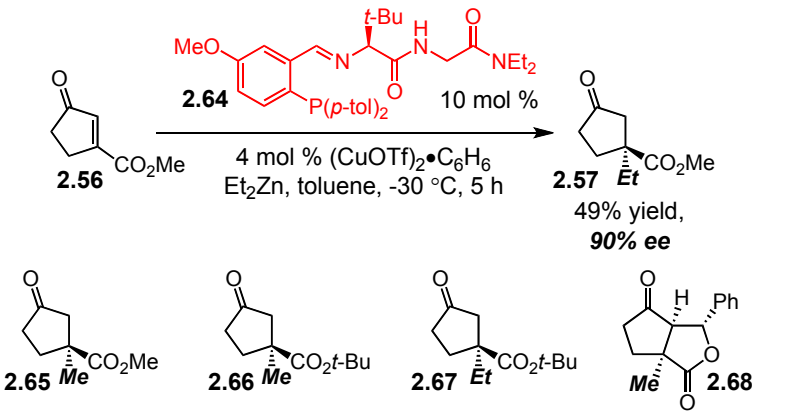
Scheme 2.9: Electronic Modifications to the Phosphine Schiff Base



As illustrated in Scheme 2.10, Cu-catalyzed ACA conjugate addition of the less reactive Me_2Zn to **2.56** provided **2.65** in low yield (8%) due to formation of the Clasien condensation byproduct (i.e., **2.63**). Since the conjugate addition reaction required higher temperatures (4 °C vs. –30 °C), the rate of Clasien condensation increased relative to the conjugate addition reaction, thus more byproduct was observed. To increase the yield of isolated product, we prepared the sterically demanding *t*-Bu ester analog of **2.56**, with the hope that the increased steric congestion around the ester unit would disfavor the formation of byproduct **2.63**. Indeed the ACA adducts from reactions of *t*-Bu ester analog of **2.56** with Me_2Zn and Et_2Zn (synthesis of **2.66** and **2.67**, respectively) were obtained in higher yield than with reactions of **2.56** (8 vs. 51% and 49 vs. 91% yield). In

addition, Cu-catalyzed ACA of Me_2Zn to **2.56** under the above-mentioned conditions in the presence of benzaldehyde led to the formation of **2.68**, which contains three contiguous stereogenic centers, in 67% yield and *91% ee as a single diastereomer*. It is likely the diastereoselectivity observed was not a consequence of a highly selective aldol reaction, but rather due to a thermodynamic preference for the observed product. The initial ACA/aldol adduct could either undergo irreversible lactonization or retroaldol/aldol reaction until the proper stereoisomer was generated that could cyclize to afford **2.68**. It is important to note that benzaldehyde was present in the reaction mixture from the beginning such that the generated zinc enolate was trapped prior to undergoing Clasien condensation.[70]

Scheme 2.10: Cu-Catalyzed ACA of Dialkylzinc Reagents to Cyclic Unsaturated Cyclic γ-Ketoesters

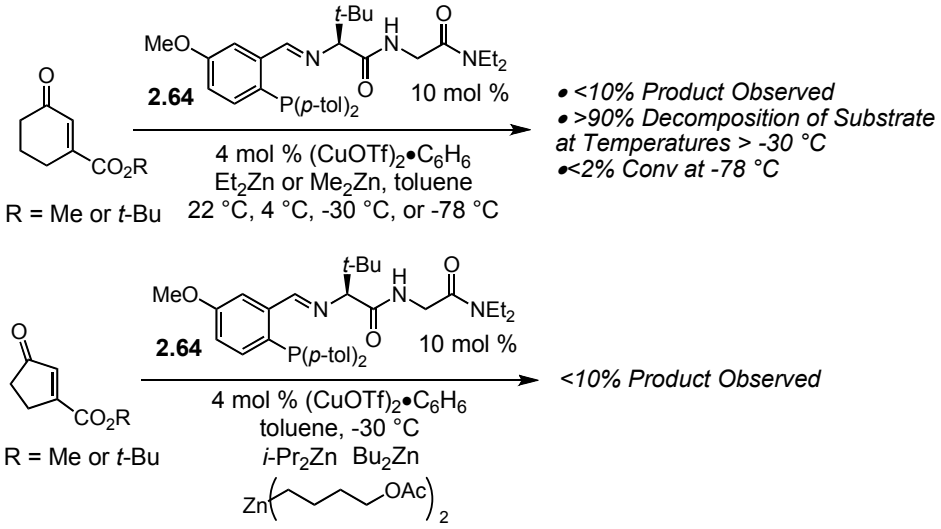


[a] ACA to **2.56** carried out in the presence of 2.0 equiv PhCHO.

(70) See Chapter 1 for a discussion regarding use of aldehydes as trapping reagent in ACA reactions.

Although we were able to obtain high selectivity and moderate yields for select substrates and dialkylzinc reagents, sterically demanding *i*-Pr_2Zn or functionalized dialkylzinc reagents proved to be poor nucleophiles for this process (<10% conv) (Scheme 2.11). Furthermore, catalytic ACA of Et_2Zn or Me_2Zn, under a variety of conditions, to six-membered analog of **2.56** resulted in decomposition or low conversion (Scheme 2.11).

Scheme 2.11: Limitations of the Current Method



The present limitations of this method and concurrent research within our laboratories involving Cu-catalyzed asymmetric allylic alkylation (AAA) with diorganozinc reagents promoted by chiral Ag(I)-*N*-heterocyclic carbene (NHC) based ligands prompted us to investigate the application of these complexes for Cu-catalyzed ACA.

2.4 *Cu-Catalyzed ACA of Diorganozinc Reagents Promoted by N-Heterocyclic Carbene (NHC) Based Ligands*

2.4.a General Characteristic of NHCs

Over the last two decades *N*-heterocyclic carbenes (NHCs) have emerged as one of the most important classes of ligands in organometallic chemistry by allowing synthetic chemists to carry out unprecedented and novel transformations once thought to be impossible.[71,72] Most notably, Ru-catalyzed olefin metathesis has benefited from the incorporation of NHC-based ligands.[73] The unique properties of NHCs have allowed these advances in synthetic chemistry to take place; the following section will outline the structural and electronic features of NHCs.

NHCs are easily prepared through deprotonation of the corresponding imidazolinium salts, which are readily available and stable organic compounds. As illustrated in Figure 2.3, several types of NHCs bearing different steric and electronic properties have been prepared.[72] Once the NHC is generated, it predominantly exists in the singlet (vs. triplet) ground state. This feature is unusual as most carbenes favor the triplet ground state. Two main characteristics force NHCs to favor a singlet state ground state. (1) In a linear carbene, the two frontier p-orbitals (p_x and p_y) are degenerate and

(71) "Ag(I) N-Heterocyclic Carbene Complexes: Synthesis, Structure, and Application," Garrison, J. C.; Youngs, W. J. *Chem. Rev*. **2005**, *105*, 3978-4008.
(72) "Stable Carbenes," Bourissou, D.; Guerret, O.; Gabbai, F. P; Bertrand, G. *Chem. Rev*. **2000**, *100*, 39-92.
(73) (a) "Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands," Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956. (b) "Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts," Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179.

thus, according to Hund's rule, the lowest energy state is a diradical (Figure 2.3, a). Upon contraction of the N-$C_{carbene}$-N angle, however, the degeneracy of the two orbitals is disrupted. The central carbon is now sp^2 hybridized and therefore the p_y (now p_π) orbital remains unchanged while the p_x orbital is stabilized by acquiring s-character (thus called the σ orbital). If the σ-p_π gap is >2 eV, the carbene is considered to have a singlet ground state and thus the electron pair resides within the lower energy σ-orbital (vs. p_π-orbital). (2) Donation from the neighboring nitrogen lone pair electrons occupies the vacant p_π orbital and thus disfavors the triplet state through electron-electron repulsion (Figure 2.3, b).

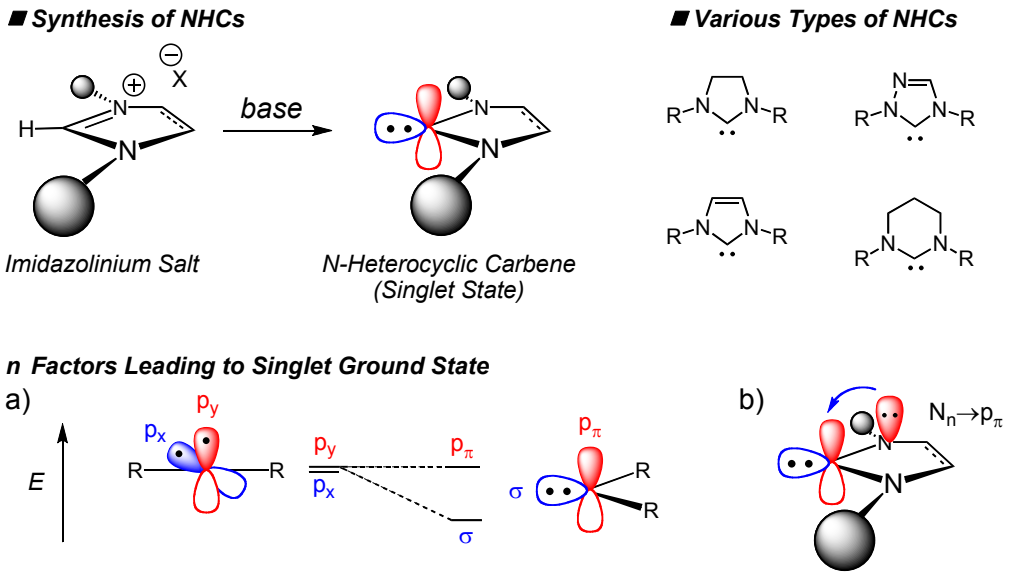
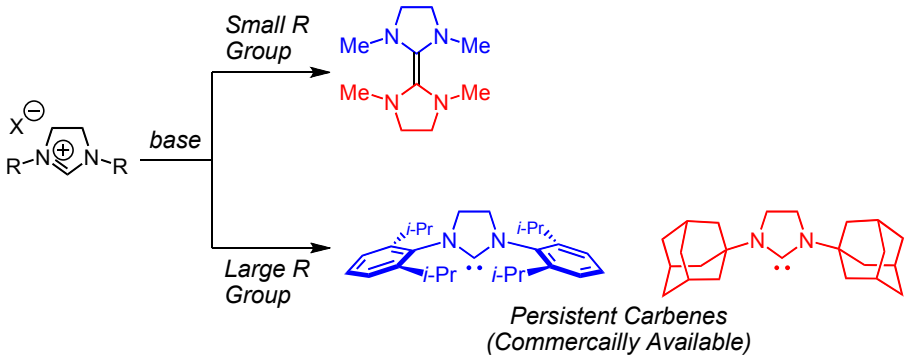


Figure 2.3: General Features of *N*-Heterocyclic Carbenes (NHCs)

Carbenes that have a singlet ground state are considered to be ambiphilic due to the vacant π-orbital and the filled σ-orbital. Due the to positive and negative nature of carbenes, dimerization leading to an olefin-containing product is often encountered

(Scheme 2.12).[74] As demonstrated by Arduengo in 1991, however, dimerization can be kinetically disfavored by sterically shielding the carbene (Scheme 2.12).[75] Consequently, several persistent NHCs are now commercially available as bench-stable solids. An alternative approach to stabilization of carbenes is though coordination to a metal salt.

Scheme 2.12: Steric Factors Leading to Stability of NHCs



Metal-NHC complexes are prepared in analogy to NHCs, except the free carbene is trapped by binding with a metal salt (Figure 2.4, a). Once bound to the metal, the NHC behaves as a strong two electron donor similar to phosphine-derived ligands.[76] NHCs, however, often form much stronger bonds with a metal, when compared to phosphines, due to the increased σ-donating nature of the carbene. NHCs were once considered to be pure σ-donors with no significant π-backdonation from the metal due to partial occupation of the vacant p_π orbital from the neighboring nitrogen lone pairs. Recent experimental and theoretical work, however, has suggested significant amounts of π-

(74) "Steric Stabilization of Nucleophilic Carbenes," Denk, M. K.; Thadani, A.; Hatano, K.; Lough, A. J. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2607-2609.
(75) "A Stable Crystalline Carbene," Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361-363.
(76) "Stereoelectronic Parameters Associated with N-Heterocyclic Carbene (NHC) Ligands: A Quest for Understanding," Díez-González, S.; Nolan, S. P. *Coord. Chem. Rev.* **2007**, *251*, 874-883.

backdonation may occur.[76,77] Due to the strong bond, [M]-NHC complexes are often stable to heat, moisture and oxygen.

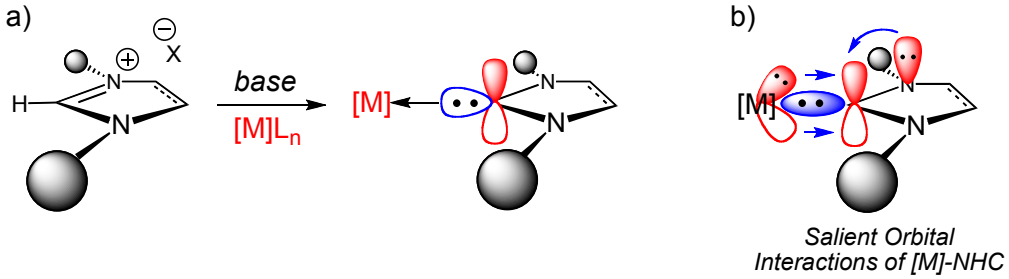


Figure 2.4: Synthesis and Orbital Interactions of [M]-NHC

An alternative route for synthesis of various [M]-NHC complexes is illustrated in Figure 2.5. Treatment of an imidazolinium salt with a silver base (i.e., Ag_2O or Ag_2CO_3) often leads to facile formation of a Ag-NHC complex. Silver-NHC complexes are frequently isolated as bench-stable solids; however, as with most Ag-complexes, sensitivity to light can be encountered. Simple treatment of the Ag-NHC complex with a variety of late transition metal salts leads to formation of the [M]-NHC complex with concomitant precipitation of AgX. While precipitation of AgX salts generally drives the transmetalation to completion, in certain cases, such as with Cu and Au, the corresponding [M]-NHC complex is more stable than the Ag-NHC complex and thus transmetalation is thermodynamically driven.[71]

(77) "N-Heterocyclic Carbene-Transition Metal Complexes: Spectroscopic and Crystallographic Analyses of π-Back-bonding Interaction," Khramov, D. M.; Lynch, V. M.; Bielwaski, C. W. *Organometallics* **2007**, *26*, 6042-6049.

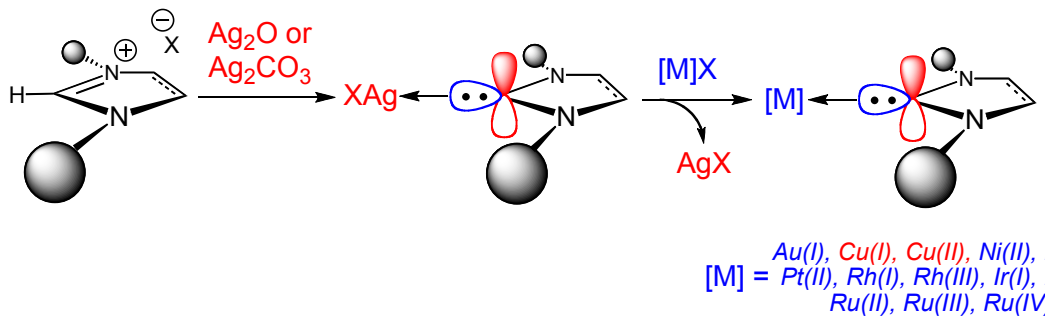


Figure 2.5: Silver-NHCs as a Synthetic Intermediate to [M]-NHCs

2.4.b Enantioselective Alkylation Reactions with Chiral Cu-NHC Complexes

2.4.b.1 Background

As with any enantioselective metal-catalyzed process, one of the greatest challenges is relay of stereochemical information from the chiral ligand scaffold to the metal center. Several classes of chiral NHC ligands have been prepared and shown to induce high levels of selectivity (Figure 2.6).[78] Type **3.I** chiral NHC bears stereogenic substituents neighboring the NHC while type **3.II** carbenes feature a chiral diamine backbone, which induces a gearing effect with groups flanking the carbene. Chiral NHCs of type **3.III** and **3.IV** are related to types **3.I** and **3.II**, except one of the substituents bears a linking atom (denoted L), thus creating a bidentate complex. It is the hope that with these complexes (**3.III** and **3.IV**) the chiral information is more effectively

(78) (a) "Chiral *N*-Heterocyclic Carbene-Transition Metal Complexes in Asymmetric Catalysis," Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951-961. (b) "Chiral N-Heterocyclic Carbenes as Stereodirecting Ligands in Asymmetric Catalysis," César, V.; Bellemin-Laponnaz, B.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619-636. (c) "Metal-mediated Asymmetric Alkylation using Chiral *N*-Heterocyclic Carbenes Derived from Chiral Amines," Douthwaite, R. E. *Coord. Chem. Rev.* **2007**, *251*, 702-717.

transferred to the metal center by rendering the complex more rigid, and in some cases by creating a stereogenic metal center.

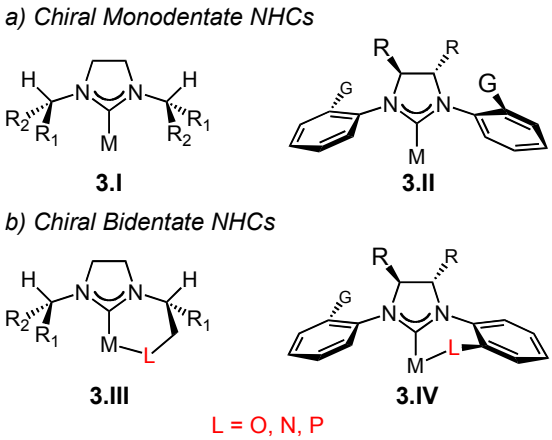
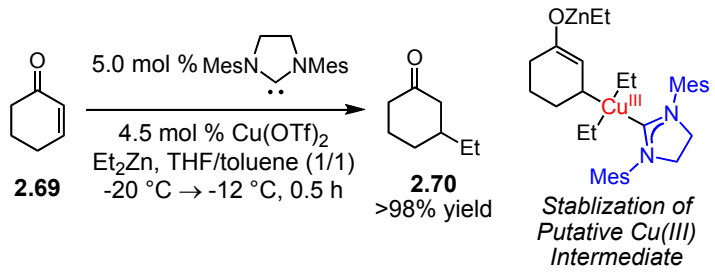


Figure 2.6: Various Types of Chiral NHCs

In 2001, Woodward and co-workers demonstrated that NHCs greatly increased the rate of Cu-catalyzed conjugate addition reactions of dialkylzinc reagents to simple unsaturated carbonyls (i.e., **2.69**, Scheme 2.13).[79] It was proposed that due to the strong electron donating nature of the NHC, the putative Cu(III) intermediate would be stabilized and thus accelerate the rate of reaction. While certainly this is not the first example of a Lewis basic ligand accelerating the rate of a conjugate addition reaction,[56] it does demonstrate that NHCs are competent ligands for this type of process.

(79) "Strong Ligand Accelerated Catalysis by an Arduengo-Type Carbene in Copper-Catalysed Conjugate Addition," Fraser, P. K.; Woodward, S. *Tetrahedron Lett.* **2001**, *42*, 2747-2749.

Scheme 2.13: Ligand Accelerated Catalysis with NHC Based Ligands

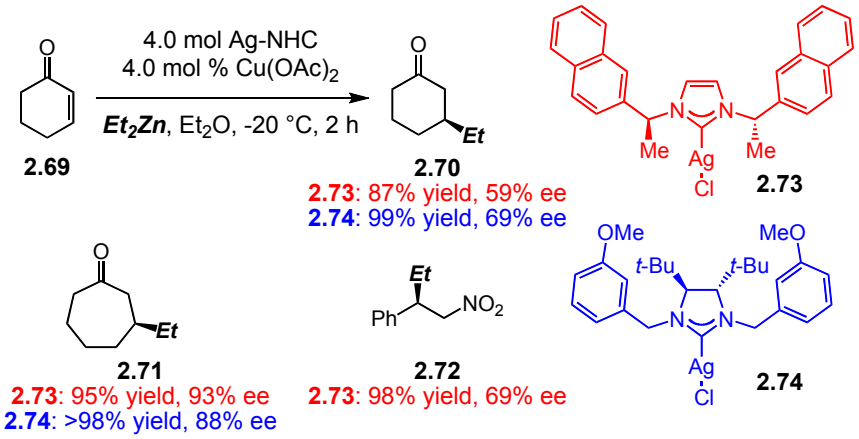


Based on Woodward's initial communication,[79] Alexakis and Mangeney developed an enantioselective variant.[80] As illustrated in Scheme 2.14, Cu-catalyzed ACA of dialkylzinc reagents to simple activated enones promoted by chiral monodentate Ag-NHC complexes **2.73** or **2.74** delivered the desired products (**2.70**-**2.72**) in moderate to excellent enantioselectivities (59-93% ee). Chiral NHCs of types **3.I** (**2.73**) and **3.II** (**2.74**) (see Figure 2.6) were found to be optimal for different substrates, highlighting the subtle interplay of substrate/chiral ligand interactions. In addition, generation of the Cu-NHC complex from the Ag-NHC complex was critical in order to achieve high efficiency and enantioselectivity. The Cu-NHC complex was prepared in situ by deprotonation of the corresponding imidazolinium salt (precursor to Ag-NHC complexes **2.73**) with *n*-BuLi and coordination of the free carbene with $Cu(OAc)_2$. This Cu-NHC catalyst was less effective than the complex derived from Ag-NHC **2.73**, delivering **2.70** in 76% yield and 38% ee. Tomioka and coworkers have also developed a Cu-catalyzed ACA of

(80) (a) "Enantioselective Copper-Catalyzed Conjugate Addition using Chiral Diaminocarbene Ligands," Gyillen, F.; Winn, C. L.; Alexakis, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2083-2086. (b) "Enantioselective Conjugate Addition of Diethylzinc using Catalytic Silver(I) Diaminocarbenes and $Cu(OTf)_2$," Pytkowicz, J.; Roland, S.; Mangeney, P. *Tetrahedron: Asymmetry*, **2001**, *12*, 2087-2089. (c) "Asymmetric Synthesis with *N*-Heterocyclic Carbenes. Application to the Copper-Catalyzed Conjugate Addition," Alexakis, A.; Winn, C. L.; Guillen, F.' Pytkowicz, J.; Roland, S.; Mangeney, P. *Avd. Synth. Catal.* **2003**, *3*, 345-348.

Grignard reagents to β-substituted cyclic enones promoted by monodentate NHC of type **3.II** (see Scheme 2.6).[66]

Scheme 2.14: Cu-Catalyzed ACA Promoted by Monodentate NHCs

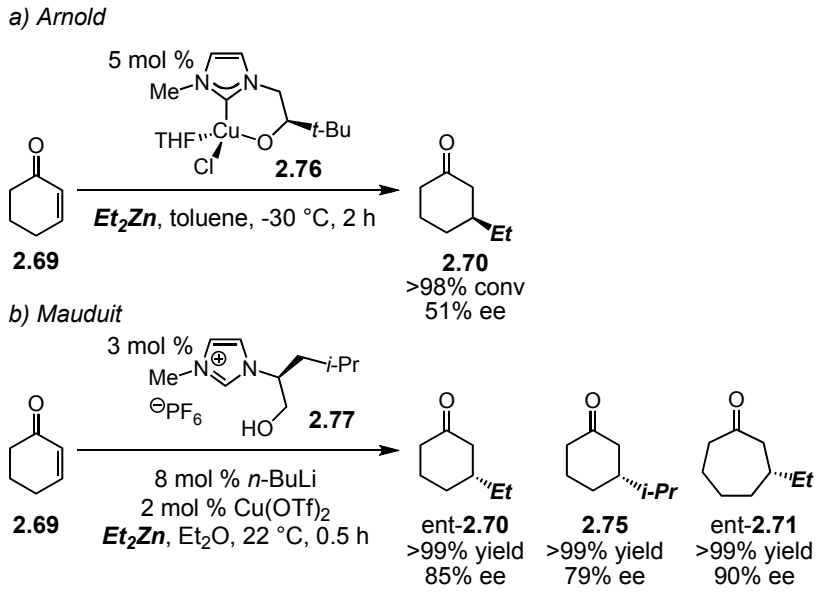


Independently, Arnold[81] and Mauduit[82] have developed amino-alcohol based bidentate NHCs for Cu-catalyzed ACA of diorganozinc regents. While chiral Cu-NHC complex **2.76**, bearing a stereogenic alkoxide unit, was only moderately selective (51% ee), leucinol-derived NHC **2.77** provided the cyclic ketones (**2.70**, **2.71**, **2.75**) in good enantioselectivities (79-90% ee). In the latter case, in situ synthesis of the chiral Cu-NHC complex was carried out though deprotonation of the imidazolinium salt with *n*-BuLi in the presence of $Cu(OTf)_2$. Use of *t*-BuMe_2Si-ether (vs. free alcohol) analog of **2.77** led to a much less selective reaction (24% ee for synthesis of **2.70**) when compared reactions promoted by **2.77**, thus highlighting the importance of the bidentate linkage. Maudiut and Alexakis, have also demonstrated that bidentate chiral ligands similar to

(81) "Asymmetric Lithium(I) and Copper(II) Alkoxy-*N*-Heterocyclic Carbene Complexes; Crystallographic Characterization and Lewis Acid Catalysis," Arnold, P. L.; Rodden, M.; Davis, K. M.; Scarisbrick, A. C.; Blake, A. J.; Wilson, C. *Chem. Commun*. **2004**, 1612-1613.
(82) "New Bidentate Alkoxy-NHC Ligands for Enantioselective Copper-Catalysed Conjugate Addition," Clavier, H.; Coutable, L.; Guillemin, J.-C.; Mauduit, M. *Tetrahedron: Asymmetry* **2005**, *16*, 921-924.

2.77 promote enantioselective conjugate additions of Grignard reagents to β-substituted cyclic enones (see Scheme 2.5).[65]

Scheme 2.15: Chiral Bidentate NHC Ligand in Cu-Catalyzed ACA

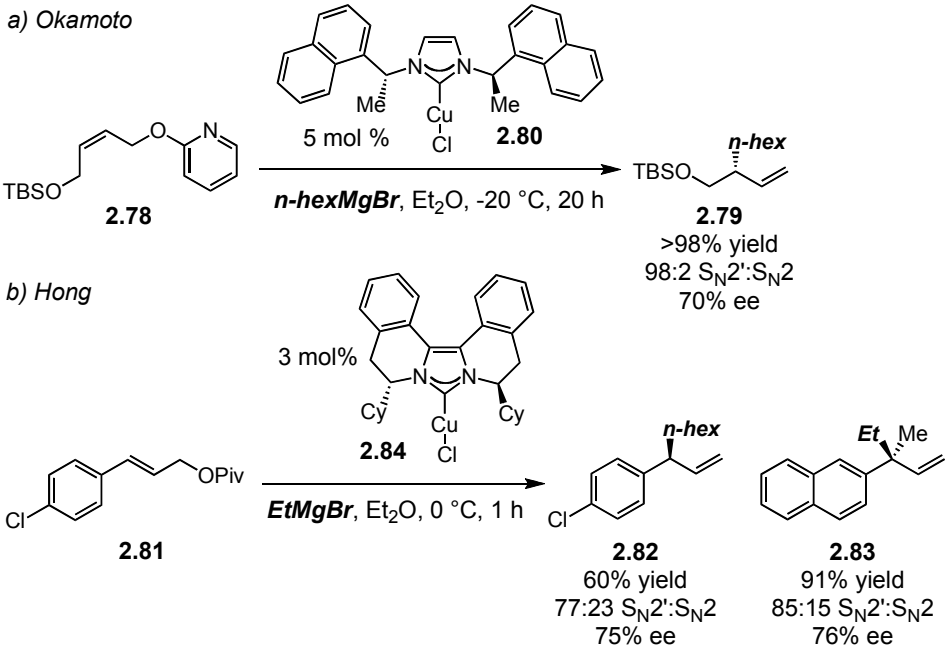


As illustrated in Scheme 2.16, Okamoto and coworkers demonstrated Cu-catalyzed asymmetric allylic alkylation (AAA) of Grignard reagents promoted by chiral monodentate NHC **2.80** to bis-allylether **2.78 (**single example).[83] Alkylation of the *E*-olefin was slightly less selective (60% ee) and resulted in formation of the opposite enantiomer. Furthermore, the 2-pyridyl ether unit was important to obtain 70% ee, as use of the corresponding -OAc derived substrate provided **2.79** in 60% ee.

(83) (a) "γ-Selective Allylic Substitution Reaction with Grignard Reagents Catalyzed by Copper *N*-Heterocyclic Carbene Complexes and its Application to Enantioselective Synthesis," Tominaga, S.; Oi, Y.; Kato, T.; An, D. K.; Okamoto, S. *Tetrahedron Lett.* **2004**, *45*, 5585-5588. (b) "Allylic Substitution Reactions with Grignard Reagents Catalyzed by Imidazolinium and 4,5-Dihydroimidazolium Carbene-CuCl Complexes," Okamoto, S.; Tominaga, S.; Saino, N.; Kase, K.; Shimoda, K. *J. Organomet. Chem.* **2005**, *690*, 6001-6007.

Hong and coworkers utilized monodentate biisoquinoline derived NHC **2.84** for Cu-catalyzed AAA of Grignard reagents to several cinamyl-based pivalates (i.e., **2.81**).[84] Moderate enantioselectivities and regioselectivities were observed for synthesis of both tertiary (**2.82**) and quaternary **(2.83**) carbon-containing products.

Scheme 2.16: Cu-Catalyzed AAA with Monodentate NHCs



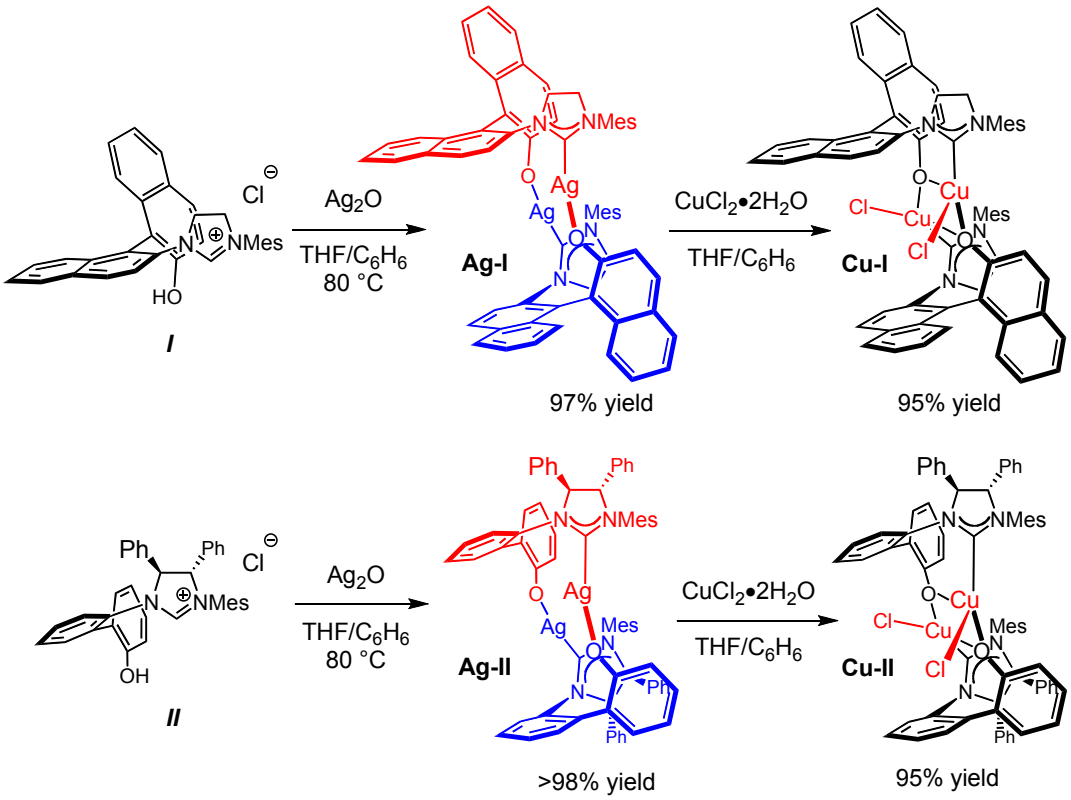
Research in our laboratories has lead to the discovery that chiral bidentate Ag-NHC complexes **Ag-I** and **Ag-II** are highly efficient and enantioselective ligands for Cu-catalyzed AAA processes (Scheme 2.17).[85] Chrial NHC precursor **I** was derived from

(84) " Development of Biisoquinoline-Based Chiral Diaminocarbene Ligands: Enantioselective S_N2' Allylic Alkylation Catalyzed by Copper-Carbene Complexes," Seo, H.; Hirsch-Weil, D.; Abboud, K. A.; Hong, S. *J. Org. Chem.* **2008**, *73*, 1983-1986.

(85) (a) "Bidentate NHC-Based Chiral Ligands for Efficient Cu-Catalyzed Enantioselective Allylic Alkylations: Structure and Activity of an Air-Stable Chiral Cu Complex," Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130-11131. (b) "A Readily Available Chiral Ag-Based N-Heterocyclic Carbene Complex for Use in Efficient and Highly Enantioselective Ru-Catalyzed Olefin Metathesis and Cu-Catalyzed Allylic Alkylation Reactions," Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877-6882.

chiral binapthyl derivative NOBIN. The NHC precursor **II** was designed to have a similar chiral pocket as **I** yet be more readily prepared and easily modified. In both cases the Ag-NHC complex was synthesized by treatment of imidazolinium salt (**I** or **II**) with Ag_2O. In the crystalline state as well as in solution, the Ag-NHC complexes **Ag-I** and **Ag-II** exist primarily as a head-to-tail dimers. Subjection of the Ag-NHC complexes to $CuCl_2 \bullet 2H_2O$ led to clean formation of Cu-NHC complexes **Cu-I** and **Cu-II** in 95% yield; these complexes also exist as head-to-tail dimers.

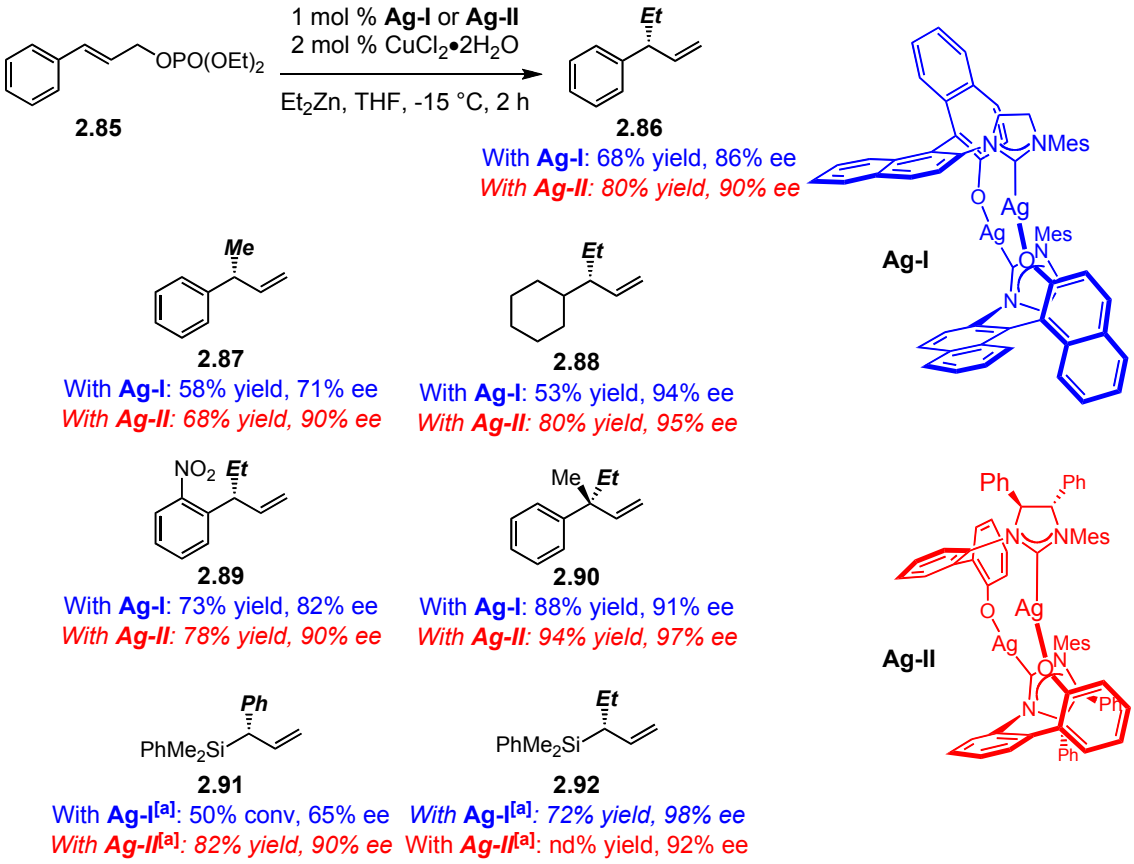
Scheme 2.17: Synthesis of Ag- and Cu-NHC complexes



(c) "Enantioselective Synthesis of Allylsilanes Bearing Tertiary and Quaternary Si-Substituted Carbons through Cu-Catalyzed Allylic Alkylations with Alkylzinc and Arylzinc Reagents," Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed*. **2007**, *46*, 4554-4558.

As illustrated in Scheme 2.18, Cu-catalyzed AAA with diorganozinc reagents proceeded efficiently (>98% conv, <24 h) with 1 mol % chiral NHC complexes **Ag-I** or **Ag-II** and 2 mol % $CuCl_2 \bullet 2H_2O$ to provide the desired products (**2.86**-**2.92**) in excellent enantioselectivities (90-98% ee). AAA of a variety of dialkylzinc reagents (Me_2Zn, Et_2Zn, Bu_2Zn, *i*-Pr_2Zn) to di- and trisubstituted allylic phosphates was carried out. In most cases, the products were generated in higher enantiomeric excess for reactions promoted by NHC **Ag-II**, when compared to processes with NHC **Ag-I**. However, AAA of dialkylzinc reagents to afford chiral allylsilanes, the NHC **Ag-I** was optimal (i.e., **2.92**). Furthermore, for the first time, highly enantioselective (90% ee) AAA of diarylzinc reagents was efficiently carried out to provide chiral allylsilanes (**2.91**).

Scheme 2.18: Cu-Catalyzed AAA with 1st and 2nd Generations NHC Ligands

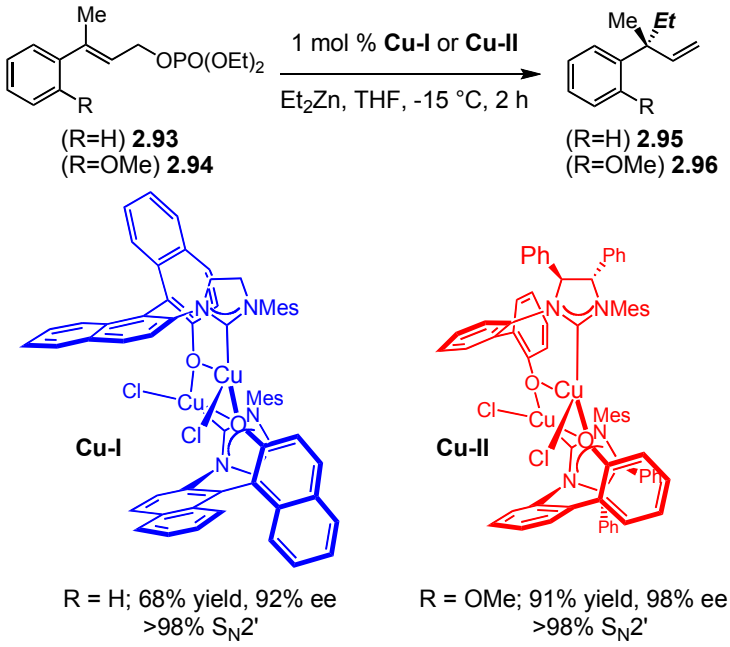


[a] Reactions carried out with 1 mol % $(CuOTf)_2•C_6H_6$

In addition, AAA was carried with isolated Cu-NHC complexes **Cu-I** and **Cu-II** to provide the products with similar enantioselectivities to reactions with in situ generated Cu-NHC complexes (Scheme 2.19). These finding suggest that the Cu-NHC complex generated in situ was the same compound as chiral Cu-NHC complexes **Cu-I** or **Cu-II**. It is important to note that it was crucial that the Cu-complex was generated by transmetalation with the Ag-complex as reactions carried out with the imidazolinium salt (carbene formation by deprotonation with R_2Zn) led to inefficient reactions. For example, Cu-catalyzed AAA of Me_2Zn to **2.85** in the presence of 1.0 mol %

imidazolinium salt **I** and 0.5 mol % $(CuOTf)_2 \bullet C_6H_6$ led to the formation of **2.86** in 65% ee (>98% conv, 1 h).

Scheme 2.19: AAA in the Presence of Cu-NHC Complexes



2.4.b.2 Cu-Catalyzed ACA to Unactivated Cyclic Enones: Synthesis of All-Carbon Quaternary Stereogenic Centers[86]

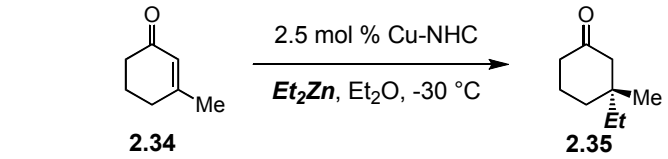
To initiate our studies on ACA of dialkylzinc reagents to unactivated β-substituted cyclic enones (i.e., **2.34**), we examined chiral Cu-NHC complexes **Cu-I** and **Cu-II**, which have been demonstrated to be efficient catalysts in AAA to afford quaternary carbon stereocenters (Scheme 2.18).[85] As illustrated in Scheme 2.20, ACA of Et_2Zn to enone **2.34** promoted by 2.5 mol % **Cu-I** or **Cu-II** provided the desired product

(86) "A Practical Method for Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers through NHC-Cu-Catalyzed Conjugate Additions of Alkyl- and Arylzinc Reagents to β-Substituted Cyclic Enones," Lee, K-s.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182-7184.

2.35 with appreciable levels of enantioselectivity (72% ee with **Cu-I**, 59% ee with **Cu-II**), albeit inefficiently (32-53% conv).[87] Further optimization revealed that ACA promoted by the corresponding NHC-Cu(I) complex, which was generated in situ from Ag-NHC complex **Ag-II** and $(CuOTf)_2 \bullet C_6H_6$ was significantly more enantioselective (93% ee) and efficient (94% conv, 6 h) than with Cu(II) based complexes (either isolated or in situ prepared from the Ag-NHC complex). The difference in reactivity between Cu(I) and Cu(II) derived complexes likely arises because of slow Cu(II)→Cu(I) reduction with alkylzinc reagents under the reaction conditions.[88]

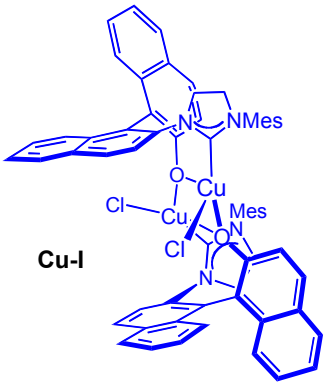
(87) Reaction carried out in THF led to <2% conv.
(88) It is likely that Cu(I) based complexes were likely responsible for C-C bond formation. For a discussion on the mechanism of Cu-promoted conjugate addition reactions, see section 2.4.b.6 and references cited therein.

Scheme 2.20: Initial Survey of Cu-NHC Complexes for ACA of Et_2Zn

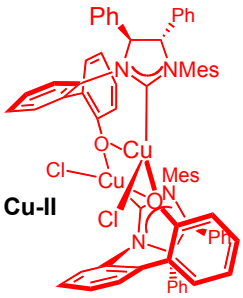


2.34 **2.35**

•Isolated Cu-NHC Complexes



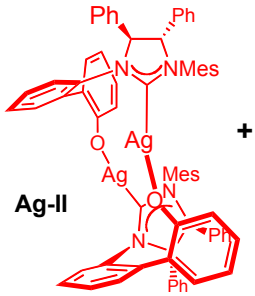
Cu-I



Cu-II

32% conv (48 h), 72% ee 53% conv (48 h), 59% ee

•In situ Generated Cu-NHC Complexes



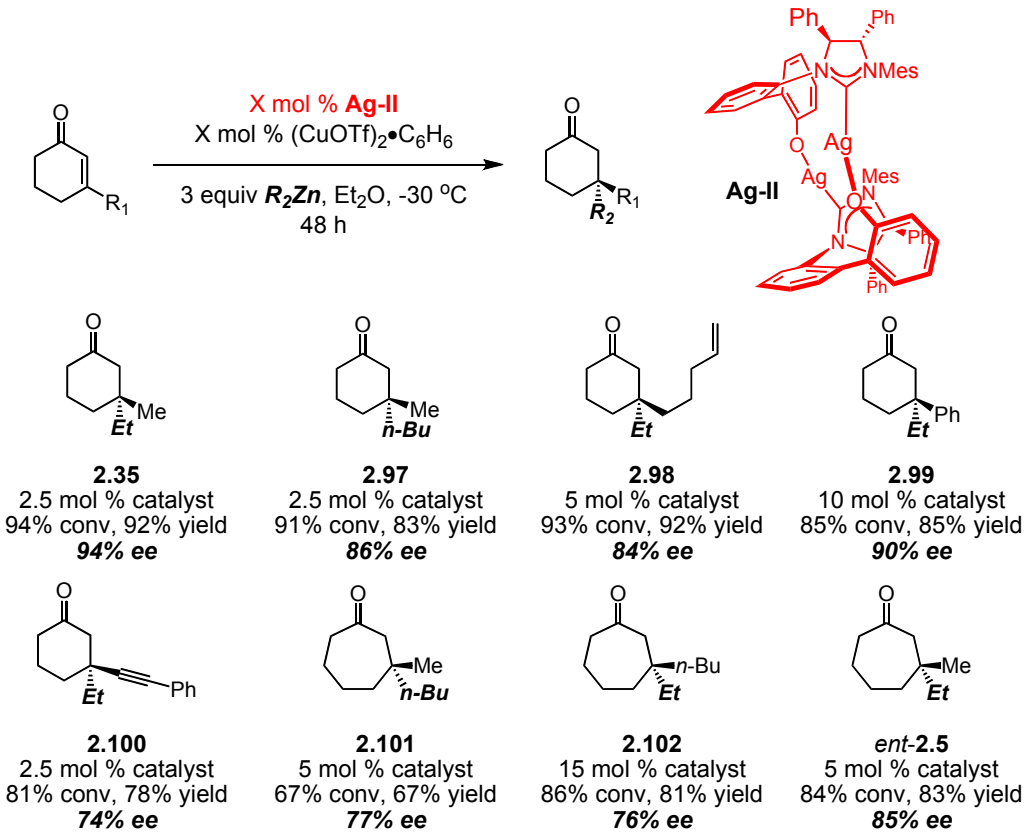
Ag-II +

$CuCl_2 \bullet 2H_2O$	56% conv (48 h), 48% ee
$Cu(OTf)_2$	45% conv (48 h), 78% ee
CuOAc	98% conv (6 h), 89% ee
CuTC	93% conv (6 h), 91% ee
$(CuOTf)_2 \bullet C_6H_6$	***98% conv (6 h), 93% ee***

Under the optimal conditions identified in Scheme 2.20, we examined the scope of the process (Scheme 2.21). Several points regarding the data in Scheme 2.21 are noteworthy: (1) A variety of β-substituted cyclohexenone substrates readily underwent highly enantioselective (generally >85% ee) additions with Et_2Zn and Bu_2Zn. Additions to sterically encumbered substrates, however, required higher catalyst loading (i.e., synthesis of **2.99**, 10 mol % catalyst). (2) Additions to β-substituted cycloheptenones were less selective than additions to six-membered ring substrates (76-85% ee) but

remained efficient (<5 mol % catalyst). Preparation of **2.102** was the exception as 15 mol % catalyst was needed to obtain 86% conv after 48 h. (3) The reactions did not give rise to significant quantities of byproducts as judged by the comparison of conversion and isolated yield.

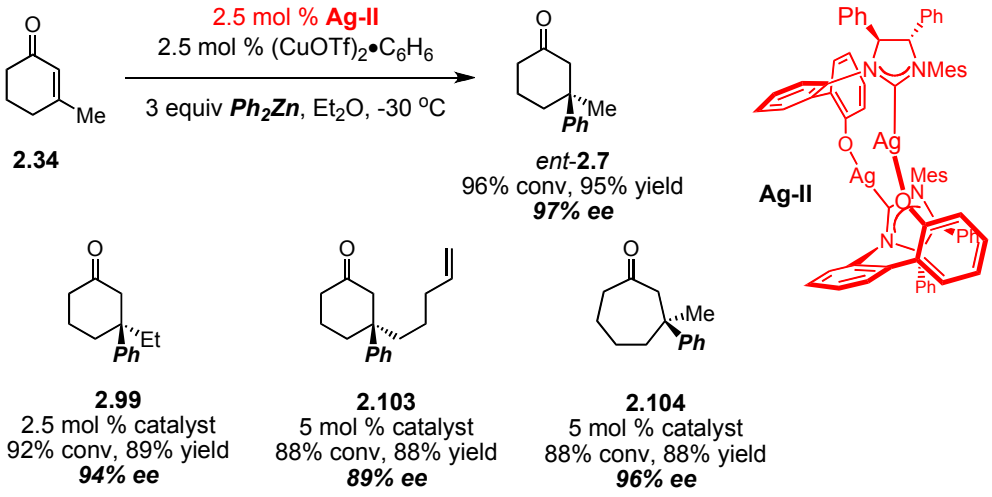
Scheme 2.21: Cu-Catalyzed ACA of Dialkylzinc Reagents



Under identical conditions presented in Scheme 2.21, highly enantioselective Cu-catalyzed ACA of Ph_2Zn was carried out (Scheme 2.22). Both cyclohexenone and cycloheptenone-derived substrates readily underwent reaction (<5 mol % catalyst) to deliver the desired products (**2.7**, **2.99**, **2.103**-**2.104**) in excellent enantioselectivity (>89%

ee).[89,90] It is important to note, that additions of dialkylzinc reagents proceeded with the opposite sense of selectivity to additions of diarylzinc reagents.[91]

Scheme 2.22: Cu-Catalyzed ACA of Diarylzinc Reagents

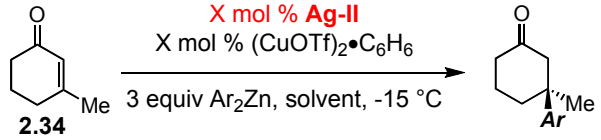


Cu-catalyzed ACA of $(p\text{-}OMeC_6H_4)_2Zn$ (**2.105**) to **2.3** promoted by **Ag-II** proceeded to provide the desired product in good enantioselectivity (76%) but with low conversion (30%) (Table 2.2, entry 1). A screen of various solvents led to the discovery that reaction in toluene led to higher conversions (57%) and enantioselectivity (89%) than reaction carried out in Et_2O (Table 2.2, entry 4). In order to enhance efficiency to synthetically useful levels (>90% conv), we increased catalyst loading (5 mol % vs. 2.5 mol %) and extended the reaction time (72 h); the cyclic ketone was obtained in 90% yield (93% conv) and 90% ee (Table 2.2, entry 5). Diarylzinc reagent **2.105** was more soluble in toluene than Et_2O, which may explain, at least partially, why higher conversion

(89) For a report detailing Rh-catalyzed ACA of arylboronic acids to afford all-carbon quaternary centers, see: ref (58b).
(90) Subsequent to our report, Mauduit and Tomioka disclosed Cu-catalyzed ACA of PhMgBr to afford all-carbon quaternary stereogenic centers, however low levels of selectivity (<60% ee) were observed, see: Scheme 2.5 and Scheme 2.6
(91) See section 2.4.b.6 for discussion.

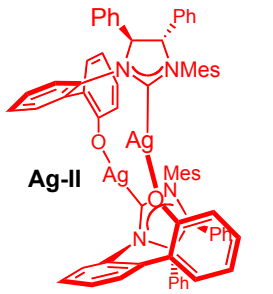
was observed. Unfortunately, Cu-catalyzed ACA of electron-deficient diarylzinc reagent **2.106** failed to deliver any desired product (<2% conv), likely due to the lower nucleophilicity associated with this diarylzinc reagent (Table 2.2, entries 6 and 7).

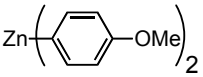
Table 2.2: Cu-Catalyzed ACA of Electronically Modified Ar_2Zn Reagents

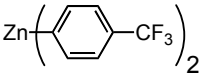


entry	Ar_2Zn	mol%	t (h)	solvent	conv (%)[a]	ee (%)[b]
1	**2.105**	2.5	18	Et_2O	30	76
2	**2.105**	2.5	18	THF	<10	nd
3	**2.105**	2.5	18	CH_2Cl_2	<10	nd
4	**2.105**	2.5	18	toluene	57	89
5	**2.105**	***5***	***72***	***toluene***	***93 (90)[c]***	***90***
6	**2.106**	5	18	Et_2O	<5	nd
7	**2.106**	5	18	toluene	<5	nd
8	Ph_2Zn	2.5	18	toluene	57	nd

[a] Determined by ^1H NMR. [b] Determined chiral HPLC analysis.
[c] Yield of isolated products in parathenses. nd = not determined



2.105 

2.106 

The limitations of this method are illustrated in Figure 2.7. Cu-catalyzed ACA of multiple diorganozinc reagents to β-substituted cyclopentenones resulted in <2% conv.[92] Furthermore, additions of the sterically demanding *i*-Pr_2Zn or the relatively unreactive Me_2Zn (compared to Et_2Zn) to any unactivated β-substituted cyclic enones were inefficient (<2% conv). Additions to cyclooctenones or use of electron-deficient

(92) Cu-catalyzed ACA to cyclopentenone-derived substrates are more challenging. For examples, see: (a) "New Chiral Oxazoline-Phosphite Ligands for the Enantioselective Copper-Catalyzed 1,4-Addition of Organozinc Reagents to Enones," Escher, I. H.; Pfaltz, A. *Tetrahedron* **2000**, *56*, 2879-2888. (b) "Modular Peptide-Based Phosphine Ligands in Asymmetric Catalysis: Efficient and Enantioselective Cu-Catalyzed Conjugate Additions to Five-, Six-, and Seven-Membered Cyclic Enones," Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755-756. (c) "Highly Enantioselective 1,4-Addition of Diorganozinc Reagents to Cyclic Enones Using Chiral Diphosphite Ligands Derived from H_8-Binaphthol," Liand, L.; Au-Yeung, T. T.-L.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 3799-3801. (d) ref (60). (e) ref (61).

diarylzinc reagents also led to inefficient processes. These limitations prompted us to explore new NHC based catalysts to carry out these difficult transformations.

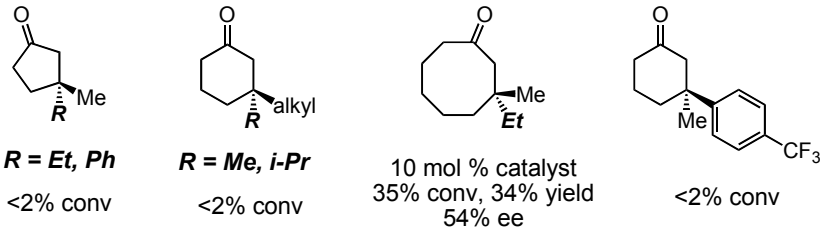


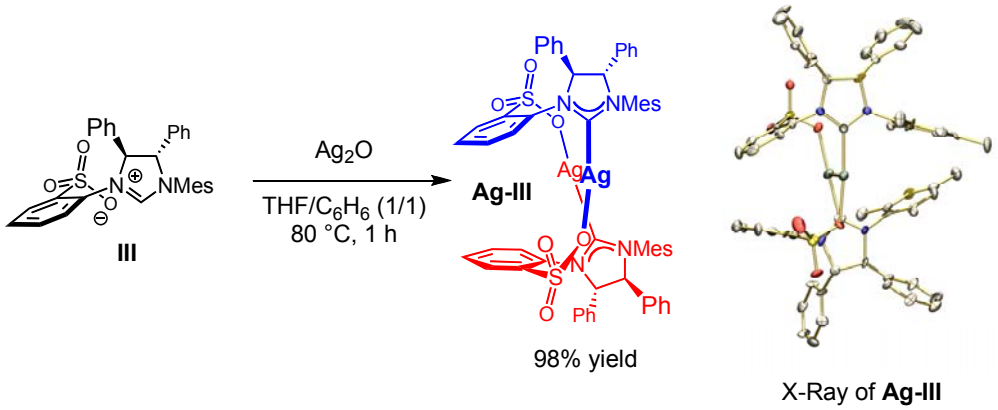
Figure 2.7: Limitations of the Current Method

2.4.b.3 Cu-Catalyzed ACA of Diorganozinc Reagents with a New Sulfonate-Based Ag-NHC Complex

Concomitant with these studies, efforts in our laboratories were directed toward synthesis and development of new classes of chiral NHC-based ligands for enantioselective Ru-catalyzed olefin metathesis. These studies led to the synthesis of sulfonate-based Ag-NHC complex **Ag-III**.[93,94] Silver-NHC complex **Ag-III** was prepared in 98% yield (>98:<2 dr) through treatment of imidazolinium salt **III** with Ag_2O. The dimeric structure of **Ag-III** was established though X-ray crystal structure analysis.

(93) For a full discussion regarding synthesis and structure of Ag-NHC **Ag-III**, see: Chapter 4
(94) These studies were carried out by Dr. Carl. A. Baxter.

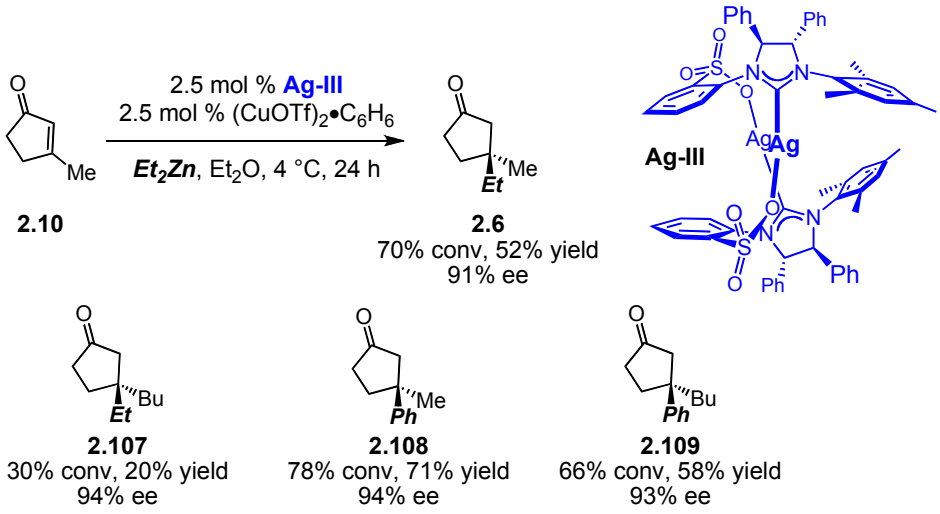
Scheme 2.23: Synthesis of 3rd Generation Ag-NHC Complex **Ag-III**



While this complex (**Ag-III**) was ineffective for Ru-catalyzed olefin metathesis reactions, we discovered that use of this ligand for Cu-catalyzed ACA reactions led to highly enantioselective processes (Scheme 2.24).[95] For the first time we could carry out additions of both Et_2Zn and Ph_2Zn to β-alkyl substituted cyclopentenones to furnish the products in excellent enantioselectivities (91-94% ee)[92] However, these processes were inefficient as incomplete reaction was observed in all cases (30-78% conv). Increased catalyst loadings, higher temperature and reaction times gave no further improvement in the efficiency of these reactions.

(95) These studies were carried out by Mikiko Akiyama.

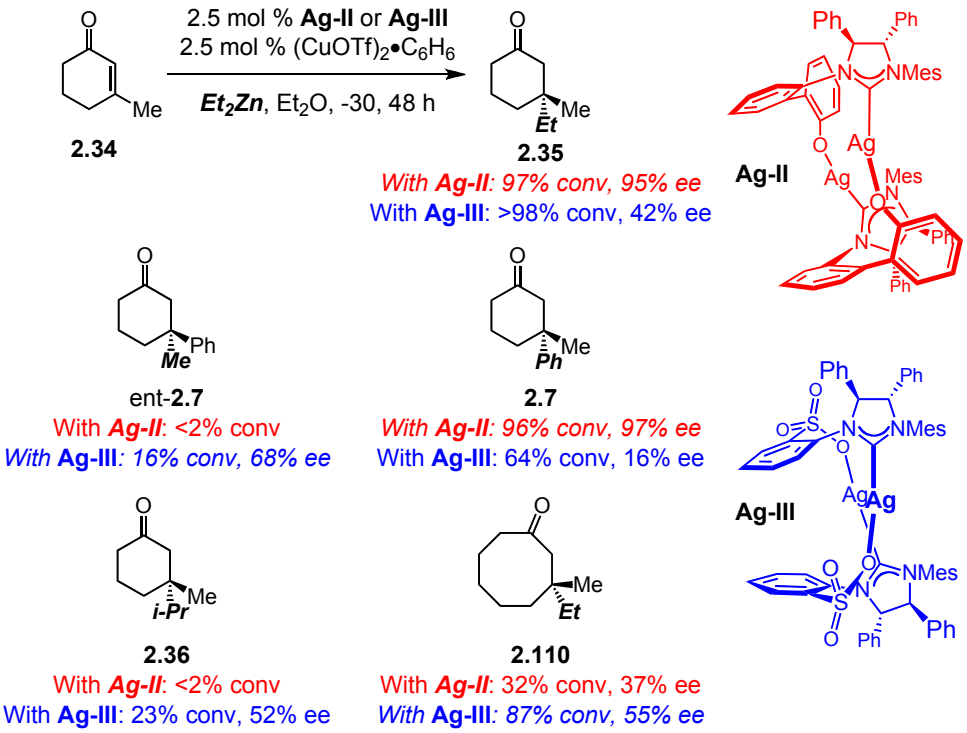
***Scheme 2.24**:* Cu-Catalyzed ACA With a New Sulfonate-Based NHC



Since the new sulfonate-containing NHC **Ag-III** gave mixed results with reactions of β-substituted cyclopentenone derivatives, we decided to investigate reactions with other difficult classes of dialkylzinc reagents and substrates.[96] As illustrated in Scheme 2.25, while Ag-NHC **Ag-III** was more efficient than Ag-NHC **Ag-II** in catalyzing the additions of dialkylzinc reagents to unactivated enones, selectivities were low in all cases. For example, Cu-catalyzed ACA of *i*-Pr_2Zn to **2.34** in the presence of Ag-NHC **Ag-II** led to <2% conv, while use of Ag-NHC **Ag-III** provided **2.36** in 52% ee (23% conv). Additions of Ph_2Zn to six-membered ring substrates (**2.34**) were less efficient and less selective with **Ag-III** than with **Ag-II** (16% vs. 97% ee). Improvement of enantioselectivities through modification of reaction conditions (solvent, temp) was unsuccessful.

(96) These studies were carried out by Kang-sang Lee.

Scheme 2.25: Comparison of Ag-NHC complexes **Ag-II** and **Ag-III**



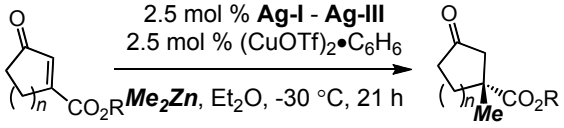
Since enantioselectivities and conversions were less than optimal in select difficult cases, we decided to investigate additions to cyclic unsaturated γ-keto esters (such as those discussed in section 2.3) with chiral bidentate NHCs. Cu-catalyzed ACA with difficult classes of unactivated enones and diorganometal reagents has been addressed through the use of triorganoaluminum reagents; these studies are discussed in Chapter 3.

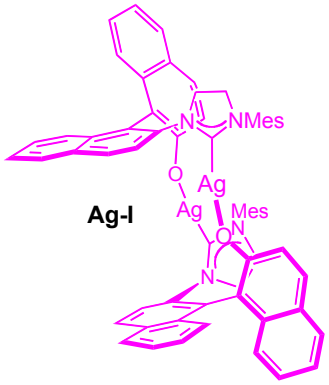
2.4.b.4 Cu-Catalyzed ACA to Cyclic Unsaturated γ-Keto Esters: Synthesis of All-Carbon Quaternary Stereogenic Centers[97]

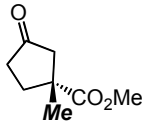
We have discovered that under the previously identified optimal conditions for Cu-catalyzed ACA of dialkylzinc reagents to cyclic β-alkyl unsaturated carbonyls promoted by Ag-NHC complex **Ag-II**, we obtained the products from alkylation with Me_2Zn of both the five- (*ent*-**2.65**-*ent*-**2.66**) and six-membered (**2.111**-**2.112**) ring γ-ketoester substrates efficiently (>98% conv, 21 h, except synthesis of *ent*-**2.66**, 30% conv) albeit with low selectivity (generally <30% ee, Scheme 2.26). In one instance, catalytic ACA provided *ent*-**2.65**, efficiently (>98% conv) and with good selectivity (85% ee). Use of NHC **Ag-I** delivered products of increased selectivity for reactions of six-membered ring substrates (**2.111** and **2.112**, 66% and 73% ee, respectively); however, efficiency was now an issue (<65% conv). In reactions with five-membered ring substrates promoted by **Ag-I**, <10% conv was observed. Further optimization revealed that sulfonate-based Ag-NHC complex (**Ag-III**) provided the desired products in higher enantiomeric purity when compared to reactions with NHCs **Ag-I** or **Ag-II**. Subsequently, we discovered that reactions carried out in *t*-BuOMe resulted in equally efficient, yet more selective reactions when compared to Et_2O (75% ee vs. 84% ee) (Table 2.3, entry 4). Reactions in coordinating solvents (THF, DME) were inefficient and less selective (Table 2.3, entries 1 and 2).

(97) "All-Carbon Quaternary Stereogenic Centers by Enantioselective Cu-Catalyzed Conjugate Additions Promoted by a Chiral N-Heterocyclic Carbene," Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097-1100.

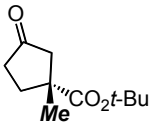
Scheme 2.26: Initial Screening with Chiral Ag-NHC Complexes for Me_2Zn Addition



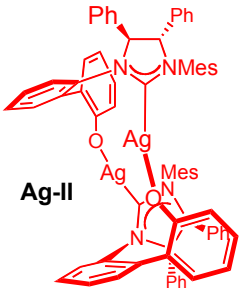


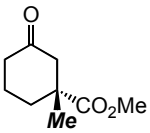


ent-**2.65**
With **Ag-I**: <10% conv
With **Ag-II**: >98% conv, 85% ee
With Ag-III: >98% conv, 83% ee

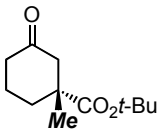


ent-**2.66**
With **Ag-I**: <10% conv
With **Ag-II**: 15% conv, 30% ee
With Ag-III: >98% conv, 84% ee





2.111
With **Ag-I**: 63% conv, 66% ee
With **Ag-II**: >98% conv, 23% ee
With Ag-III: >98% conv, 75% ee



2.112
With **Ag-I**: 60% conv, 73% ee
With **Ag-II**: >98% conv, 33% ee
With Ag-III: >98% conv, 75% ee

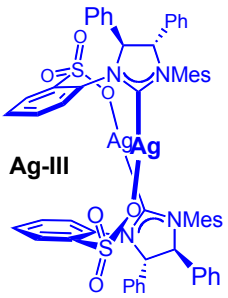
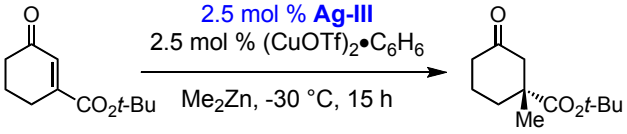


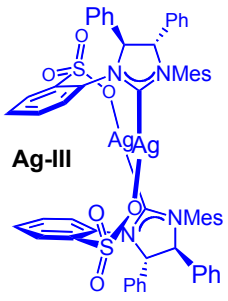
Table 2.3: Optimization of the Reaction Medium



2.113 **2.112**

entry	solvent	conv (%)[a]	ee (%)[b]
1	THF	44	<10
2	DME	84	55
3	Et_2O	>98	75
4	***t-BuOMe***	***>98***	***84***

[a] Determined by 400 MHz ^{1}H NMR analysis of the unpurified reaction mixtures. [b] Determined by chiral GLC analysis.

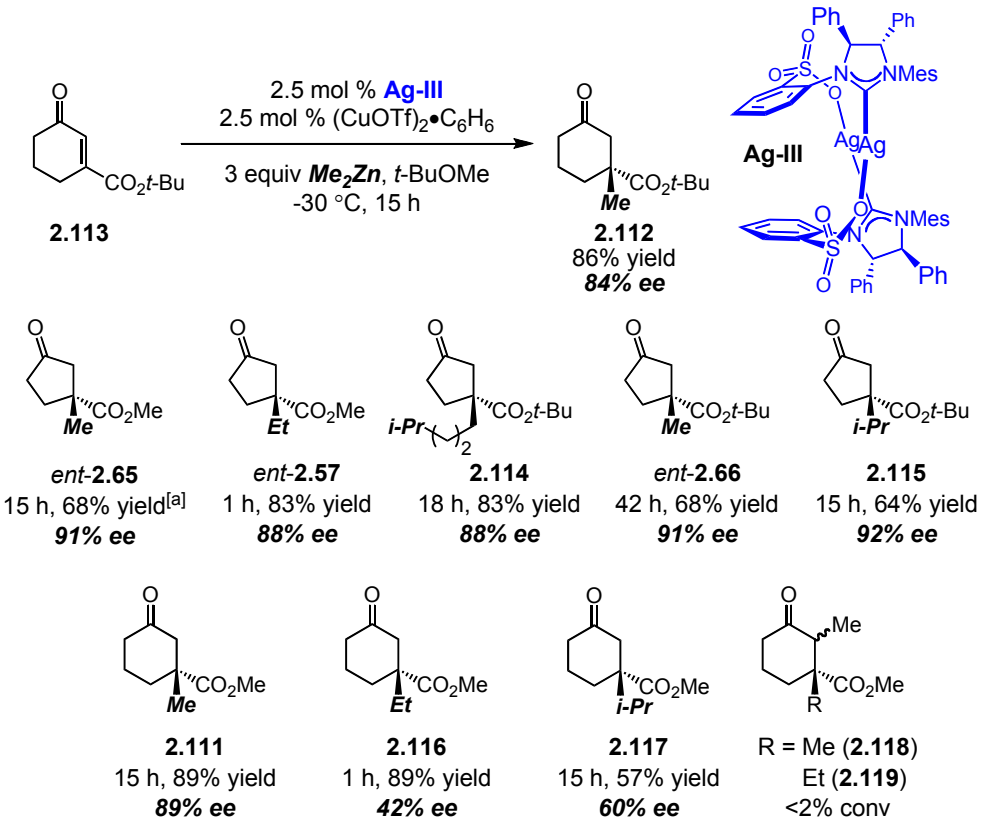


Ag-III

Results for Cu-catalyzed ACA of dialkylzinc reagents to cyclic unsaturated γ-ketoesters are summarized in Scheme 2.27. Several points regarding the ACA reactions are worthy of mention: (1) Additions of Me_2Zn to methyl and *t*-Bu ester-derived five- and six-membered ring substrates underwent highly efficient and selective additions (>84% ee). (2) *i*-Pr_2Zn, Et_2Zn and $Zn((CH_2)_3CH(CH_3)_2)_2$ were suitable nucleophiles for additions to five-membered ring substrates (88-92% ee); however, reactions with six-membered ring substrates resulted in less selective processes (<60% ee). (3) Varying the optimal reaction temperature (-30 ^oC) led to lower enantioselectivity. For example, Cu-catalyzed ACA of Et_2Zn at –78 ^oC or –15 ^oC provided **2.116** with 35% or 86% ee, respectively. (4) Additions to provide *ent*-**2.65** required higher catalyst loading (5 vs. 2.5 mol %) and excess Me_2Zn (6 vs. 3 equiv) to reduce the formation of a Clasien condensation side product (analogous to **2.63**, Scheme 2.9). (5) A limitations of this method was discovered when attempts to prepare **2.118** or **2.119** through additions of

either Me_2Zn or Et_2Zn to the corresponding tetrasubstituted olefin resulted in <2% conversion after 24 h at –30 °C.

Scheme 2.27: Cu-Catalyzed ACA of Dialkylzinc Reagents to Cyclic Unsaturated γ-Ketoesters: Scope and Limitations



[a] 5 mol % catalyst and 6 equiv Me_2Zn was used.

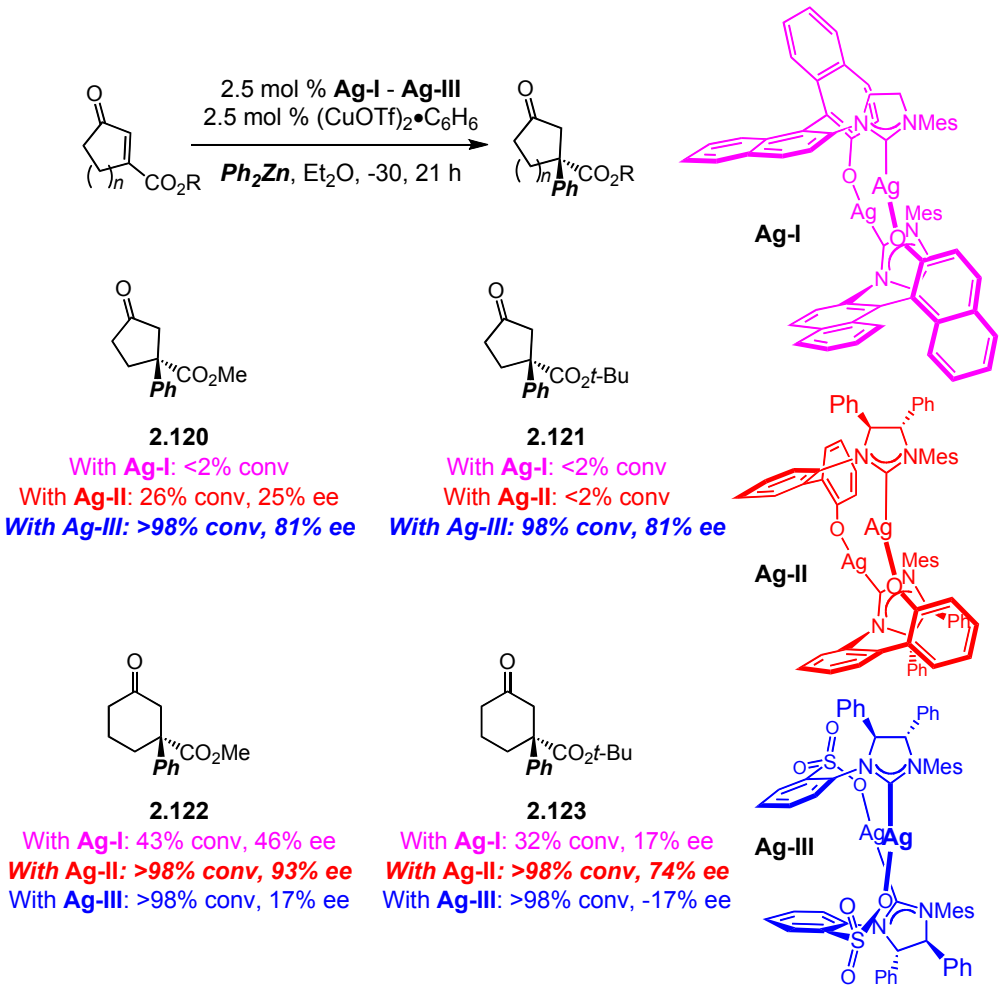
Styrene has been shown to improve the enantioselectivity in Cu-catalyzed ACA of dialkylzinc reagents to α-halo enones by acting as a radical scavenger.[98] We tested the effect of styrene as an additive (5 equiv) in our ACA reactions shown in Scheme 2.27.

(98) "Asymmetric Conjugate Addition to α-Halo Enones: Dramatic Effect of Styrene on the Enantioselectivity," Li, K.; Alexakis, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7600-7603.

We observed increased enantioselectivity in one case (73% ee vs. 60% ee, for preparation of **2.117**), however there was no significant change in the remaining cases.

Related to our studies illustrated in Scheme 2.22, we have carried out additions of Ph_2Zn to cyclic unsaturated γ-ketoesters (Scheme 2.28). A survey of chiral NHCs **Ag-I**, **Ag-II** and **Ag-III** revealed that a different ligand was optimal for five- vs. six-membered ring substrates. In the case of five-membered ring enones, NHC **Ag-III** was optimal (>98% conv, 81% ee for synthesis of **2.120** and **2.121**) whereas <30% conversion was observed in reactions with NHCs **Ag-I** or **Ag-II**. Six-membered ring substrates, however, required the use of NHC **Ag-II** to obtain high enantioselectivities (formation of **2.122** and **2.123**). Reactions with NHCs **Ag-I** or **Ag-III** provided the products in low efficiency (32-43% conv) or low selectivity (<20% ee), respectively. Attempts to increase the selectivity through the use of *t*-BuOMe (vs. Et_2O) resulted in less efficient and selective reactions. For example, reaction carried out in *t*-BuOMe delivered **2.123** in 57% ee (57% conv, 24 h). Catalytic ACAs performed in coordinating solvents led to low conversion of substrate (<30% conv with THF, DME).

Scheme 2.28: Ph_2Zn Addition to γ-Ketoesters with Chiral Ag-NHC Complexes



2.4.b.5 Functionalizations of the ACA Adducts and Issues of Practicality

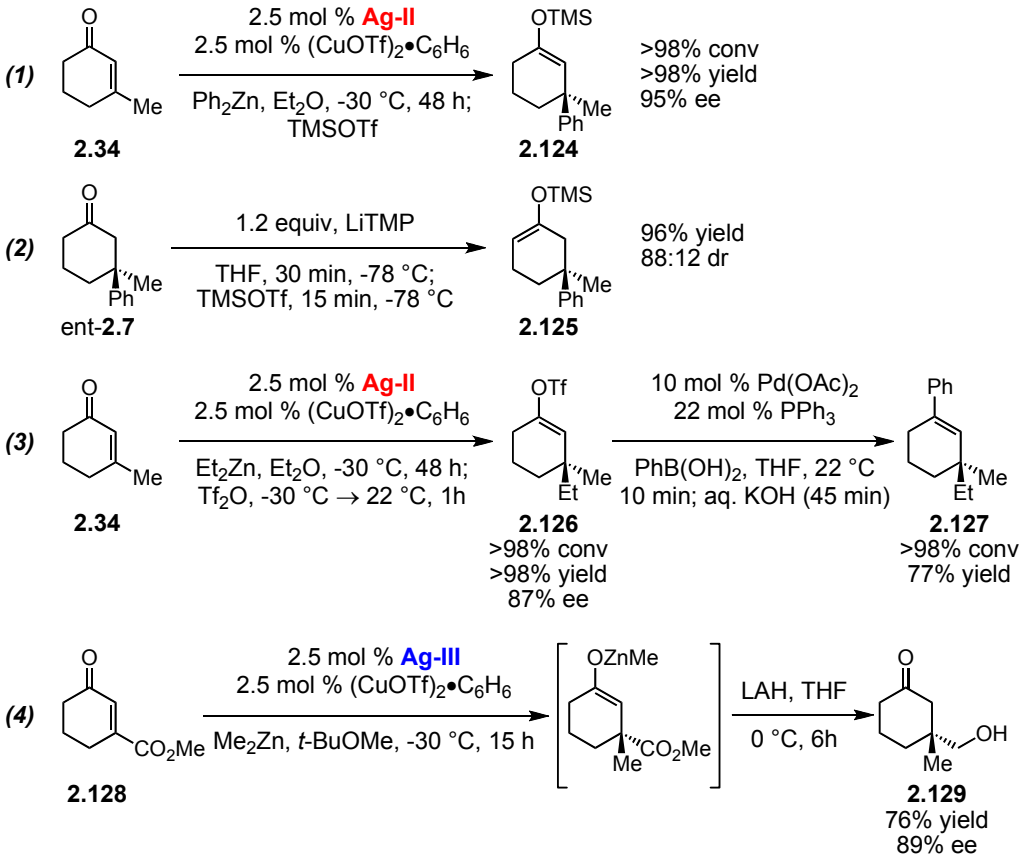
One of the most important, and often overlooked, features of conjugate addition reactions is the stereoselective generation of an enolate prior to quenching of the reaction upon aqueous workup.[99] As illustrated in Scheme 2.29, eq (1), the generated Zn-enolate can be trapped with TMSOTf to afford enol silane **2.124** in >98% yield, 95% ee and as a

(99) (a) "Tandem Asymmetric Conjugate Addition-Silylation of Enantiomerically Enriched Zinc Enolates. Synthetic Importance and Mechanistic Implications," Knopff, O.; Alexakis, A. *Org. Lett.* **2002**, *4*, 3835-3837. (b) ref (60).

single regioisomer. To obtain the other regioisomeric enolate, treatment of the ACA product (ent-**2.7**) with LiTMP and sequential trapping with TMSOTf generated an 88:12 mixture of **2.125**and **2.124** in 96% combined yield (Scheme 2.29, eq (2)). The Zn-enolate could also be quenched with Tf_2O to afford enoltriflate **2.126** in >98% yield and 87% ee, which could be subjected to a variety of transformations; Suzuki-Miyura coupling to furnish **2.127** is illustrative (Scheme 2.29, eq (3)).

One of the notable features of the methodology presented in Scheme 2.27-2.28, was the fact that the products bear a synthetically versatile ester substituent. However, selective functionalization of the ester group in the presence of the more reactive ketone would be difficult without resorting to multi-step protocols. As illustrated in Scheme 2.29, eq (4), we have demonstrated that by taking advantage of the generated zinc enolate, which effectively masks the more reactive ketone, facile reduction of the ester could be carried out with LAH to provide **2.129** in 76% yield.

Scheme 2.29: Functionalization of the ACA Products

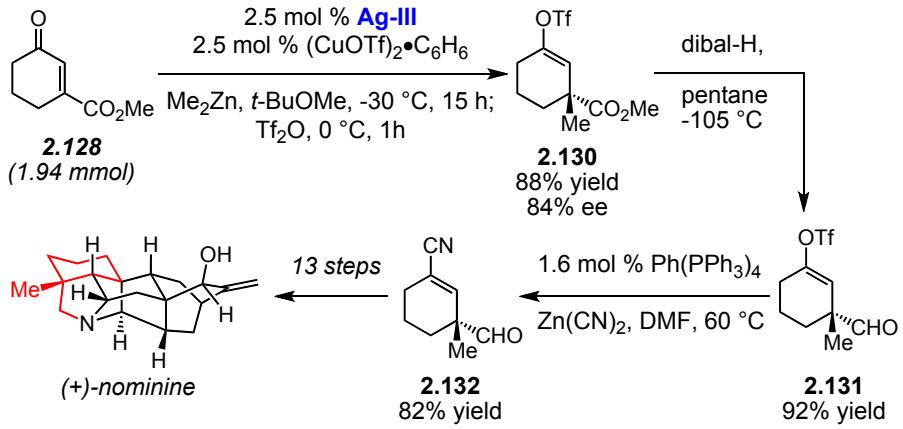


In 2007, Gin and coworkers reported an enantioselective total synthesis of hetisine alkaloid (+)-nominine featuring Cu-catalyzed ACA methodology (Scheme 2.30).[100] In the stereodetermining step, enantioselective addition of Me_2Zn followed by trapping of the derived Zn-enolate with Tf_2O provided enoltriflate **2.130** in 88% yield and 84% ee. This study also served to demonstrate that these conjugate addition reactions could be carried out on larger scale (1.94 vs. 0.1 mmol) with similar efficiency and selectivitity. Reduction of the ester group with dibal-H followed by Pd-catalyzed

(100) "Asymmetric Synthetic Access to the Hetisine Alkaloids: Total Synthesis of (+)-Nominine," Peese, K. M.; Gin, D. Y. *Chem. Eur. J.* **2008**, *14*, 1654-1665.

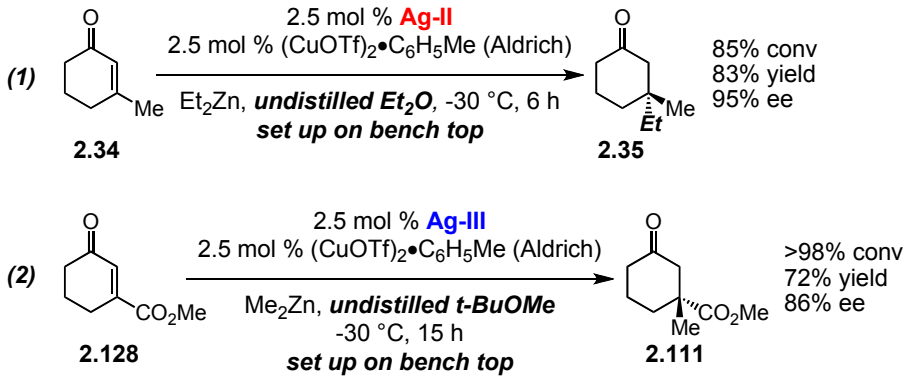
coupling of the enol triflate with $Zn(CN)_2$ furnished ene-nitrile **2.132** in 75% yield over two steps. This material was elaborated further to afford (+)-nominine in 13 steps.

Scheme 2.30: Enantioselective Total Synthesis of (+)-Nominine Reported by Gin and Coworkers Featuring Cu-Catalyzed ACA of Me_2Zn to **2.128**



The practicality of the ACA methods involving chiral NHC-based catalysts is illustrated in Scheme 2.31. Reactions could be carried out with commercially available $(CuOTf)_2•C_6H_5CH_3$ (Aldrich, not purified), in undistilled solvent and set up on a bench top with minimal loss in selectivity or efficiency. Furthermore, the reactions were amenable to scale up. For example, conjugate addition of Et_2Zn to **2.34** in the presence of 2.5 mol % NHC **Ag-II** and 2.5 mol % $(CuOTf)_2•C_6H_6$ at –40 °C performed on 0.5 g scale delivered cyclic ketone **2.35** in 87% ee and >98% yield.

Scheme 2.31: Ease of Operation

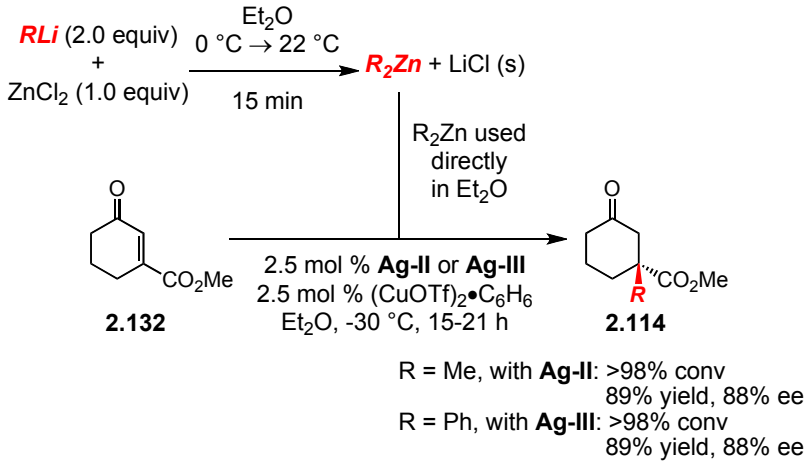


Due to the high cost of dialkylzinc reagents, especially Me_2Zn and Ph_2Zn, we sought to render the method more practical by preparing the nucleophile in situ from inexpensive lithium reagents and $ZnCl_2$ (Scheme 2.32).[101] In practice, as illustrated in Scheme 2.32, this approach proved effective as well as operationally simple. A solution of RLi in Et_2O (Aldrich) was added to a solution of $ZnCl_2$ (Strem) in Et_2O at 0 °C and allowed to warm to 22 °C over 15 min. The resulting mixture of LiCl (s) and R_2Zn in Et_2O was centrifuged to assist in settling of solid LiCl. The clear solution of R_2Zn was then used directly in Cu-catalyzed ACA reactions. A few points regarding Scheme 2.32 are noteworthy: (1) Both Me_2Zn and Ph_2Zn could be prepared in situ and used for catalytic ACA with a similar degree of efficiency and selectivity when compared to use of isolated zinc reagents. (2) When Me_2Zn was prepared in *t*-BuOMe, low conversion (60%) was observed, most likely due to incomplete formation of Me_2Zn ($ZnCl_2$ is less soluble in *t*-BuOMe than in Et_2O). (3) The product was generated in higher enantiomeric

(101) (a) "Highly Enantioselective Cu-Catalysed Asymmetric 1,4-Addition of Diphenylzinc to Cyclohexenone," Peña, D.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun*, **2004**, 1836-1837. (b) "From Aryl Bromides to Enantioenriched Benzylic Alcohols in a Single Flask: Catalytic Asymmetric Arylation of Aldehydes," Kim, J. G.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4175-4178.

purity when Me_2Zn was prepared in situ (88% ee) than when commercial grade Me_2Zn was employed (75% ee). We reasoned that this was due to small amounts of LiCl and/or $ZnCl_2$ present in the ACA reaction. However, control experiments revealed that either salt, as an additive, had no substantial effect on the reaction outcome.

Scheme 2.32: In Situ Generation/Catalytic ACA of Diorganozinc Reagent



2.4.b.6 Working Mechanistic Models

The mechanism of stoichiometric Cu-promoted conjugate addition of organometal reagents has been the subject of numerous reports.[102,103] In general, a simplified

(102) For reviews, see: (a) "Wherefore Art Thou Copper? Structure and Reaction Mechanism of Organocuprate Clusters in Organic Chemistry," Nakamura, E.; Mori, S. *Angew. Chem.* **2000**, *39*, 3750-3771. (b) "Decoding the 'Black Box' Reactivity that is Organocuprate Conjugate Addition Chemistry," Woodward, S. *Chem. Soc. Rev.* **2000**, *29*, 393-401.

(103) Several reports have detailed the mechanism of Cu-catalyzed conjugate addition. These studies are undoubtedly system specific. (a) "1,4-Addition of Diorganozincs to α,β-Unsaturated Ketones Catalyzed by a Copper(I)-Sulfamide Combined System," Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 999-1014. (b) "On the Role of P^{III} Ligands in the Conjugate Addition of Diorganozinc Derivatives to Enones," Pfretzchner, T.; Kleemann, L; Janza, B.; Harms, K.; Schrader, T. *Chem. Eur. J.* **2004**, *10*, 6048-6057. (c) "Copper Catalysed 1,4-Addition of Organozinc Reagents to α,β-Unsaturated Carbonyl Compounds: A Mechanism Investigation," Gallo, E.; Ragaini, F.; Bilello, L.; Cenini, S.; Gennari, C.; Piarulli, U. *J. Organomet. Chem.* **2004**, *689*, 2169-2176. (d) "On the Mechanism of the Copper-Catalyzed Enantioselective 1,4-Addition of Grignard Reagents to α,β-Unsaturated Carbonyl Compounds," Harutyunyuan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.;

mechanism consists of four distinct steps: (1) cuprate formation, (2) olefin coordination,[104] (3) oxidative addition[105] and (4) rate-limiting reductive elimination.[106] Based on these studies, a catalytic cycle, incorporating a bidentate NHC ligand, is presented in Scheme 2.33.

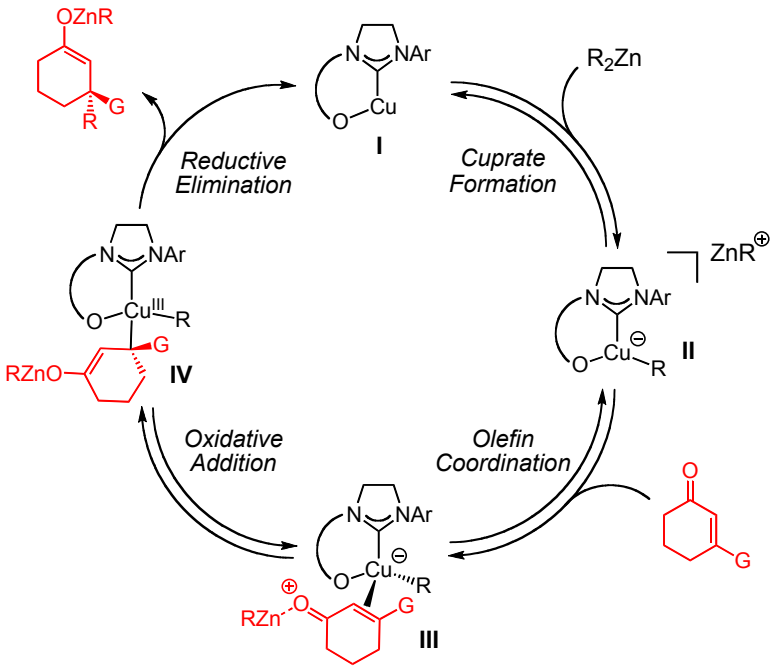
Minnaard, A. J.; Feringa. B. L. *J. Am. Chem. Soc.* **2006**, *128*, 9103-9118. (e) "Influence of Copper Salts, Solvents, and Ligands on the Structures of Precatalytic Phosphoramidite Copper Complexes for Conjugate Addition Reactions," Zhang, H.; Gschwind, R. M. *Chem. Eur. J.* **2007**, *13,* 6691-6700.

(104) For a recent reports regarding the nature of the Cu-enone complex, see: "Rapid-Injection NMR Study of Iodo- and Cyano-Gilman Reagents with 2-Cyclohexenone: Observation of π-Complexes and Their Rates of Formation," Bertz, S. H.; Carlin, C. M.; Deadwyler, D. A.; Murphy, M. D.; Ogle, C. A.; Seagle, P. H. *J. Am. Chem. Soc.* **2002**, *124*, 13650-13651.

(105) For recent studies detailing the nature of the Cu(III) intermediate, see: (a) Rapid Injection NMR in Mechanistic Organocopper Chemistry. Preparation of the Elusive Copper(III) Intermediate," Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A.; Taylor, B. J. *J. Am. Chem. Soc.* **2007**, *129*, 7208-7209. (b) Organocuprate Conjugate Addition: The Square-Planer 'Cu^{III}' Intermediate," Hu, H.; Snyder, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 7210-7211. (c) "Neutral Organocopper(III) Complexes," Bartholomew, E. R.; Bertz, S. H.; Cope, S.; Dorton, D. C.' Murphy, M.; Ogle, C. A. *Chem. Commun.* **2008**, 1176-1177. (d) "Preparation of s- and p-Allylcopper(III) Intermediates in S_N2 and S_N2' Reactions of Organocuprate(I) Reagents with Allylic Substrates," Bartholomew, E. R.; Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A. *J. Am. Chem. Soc.* **2008**, *130*, 11244-11245.

(106) (a) "^{13}C Kinetic Isotope Effects for the Addition of Lithium Dibutylcuprate to Cyclohexenone. Reductive Elimination is Rate-Determining," Frantz, D. E.; Singleton. D. A.; Snyder, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 3383-3384. (b) "Reaction Pathway of the Conjugate Addition of Lithium Organocuprate Clusters to Acrolein," Nakamura, E.; Mori, S.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, *119*, 4900-4910. (c) "Density Functional Studies on Conjugate Addition of $(Me_2CuLi)_2$ to Cyclohexenone: Stereoselectivity and Rate-Determining Step," Mori, S.; Nakamura, E. *Chem. Eur. J.* **1999**, *5*, 1534-1543.

Scheme 2.33: General Catalytic Cycle for Cu-Catalyzed ACA



The studies in sections 2.4.b.2-2.4.b.4 illustrated that bidentate NHC-Cu complexes accelerate the rate of conjugate addition reactions compared to monodentate phosphorous-based ligands.[57,60-61] Based on studies carried out independently by Nakamura, Schleyer and Snyder,[107] we propose that the bidentate NHC ligand "thermodynamically stabilizes the Cu(III) intermediate, while keeping it kinetically labile."[107b] (1) The increased thermodynamic stability of the NHC-Cu(III) intermediate **IV** arises from the strong σ-donating nature of the NHC. Thus, the equilibrium of the oxidative addition step is shifted towards Cu(III) intermediate **IV**. Furthermore, the NHC

(107) (a) "Computational Evidence for the Existence of Cu^{III} Intermediates in Addition and Substitution Reactions with Dialkylcuprates," Dorigo, A. E.; Wanner, J.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Eng.* **1995**, *34*, 476-478. (b) Mechanism of Lithium Cuprate Conjugate Addition: Neutral Tetracoordinate Cu^{I} Cuprates as Essential Intermediates," Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11025-11026. (c) Complexation of Lewis Acid with Trialkylcopper(III): On the Origin of BF_3-Accerleration of Cuprate Conjugate Addition," Nakamura, E.; Yamanaka, M.; Mori, S. *J. Am. Chem. Soc.* **2000**, *122*, 1826-1827.

exerts a strong *trans*-influence and weakens the corresponding Cu-R bond, thus allowing for more facile reductive elimination.[108] This phenomenon is illustrated in Figure 2.8, Lewis base activation. (2) Calculations carried out by Nakamura suggest that Cu(III) intermediates of type MeSCuMe(allyl) (analogous to **IV)** undergo reductive elimination more readily than MeCuMe(allyl) based Cu(III) species.[109] We propose that the less electron-donating nature of an oxygen atom (in the cases of NHC **Ag-I**-**Ag-III**), compared to carbon, renders the Cu(III) intermediate more electron deficient and thus more prone to undergo reductive elimination. For this reason the it is likely that the less electron donating sulfonate unit of **Ag-III**, relative to the phenoxy moiety of **Ag-II**, is at least one reason for the increased reactivity observed with reactions promoted by **Ag-III**, compared to **Ag-II**.

(108) At this time, it remains unclear if there is any significant difference in the donorability between the NHC unit of **Ag-II** and **Ag-III**. For a brief discussion regarding the electronic characteristic of **Ag-III**, see: Chapter 4.

(109) "Thermodynamic and Kinetic Control in Selective Ligand Transfer in Conjugate Addition of Mixed Organocuprate Me(X)CuLi," Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 4697-4706.

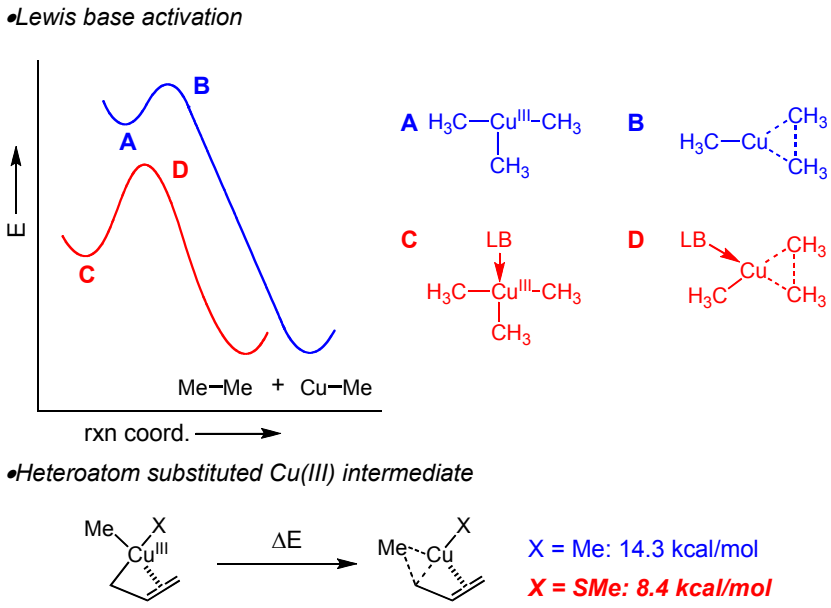
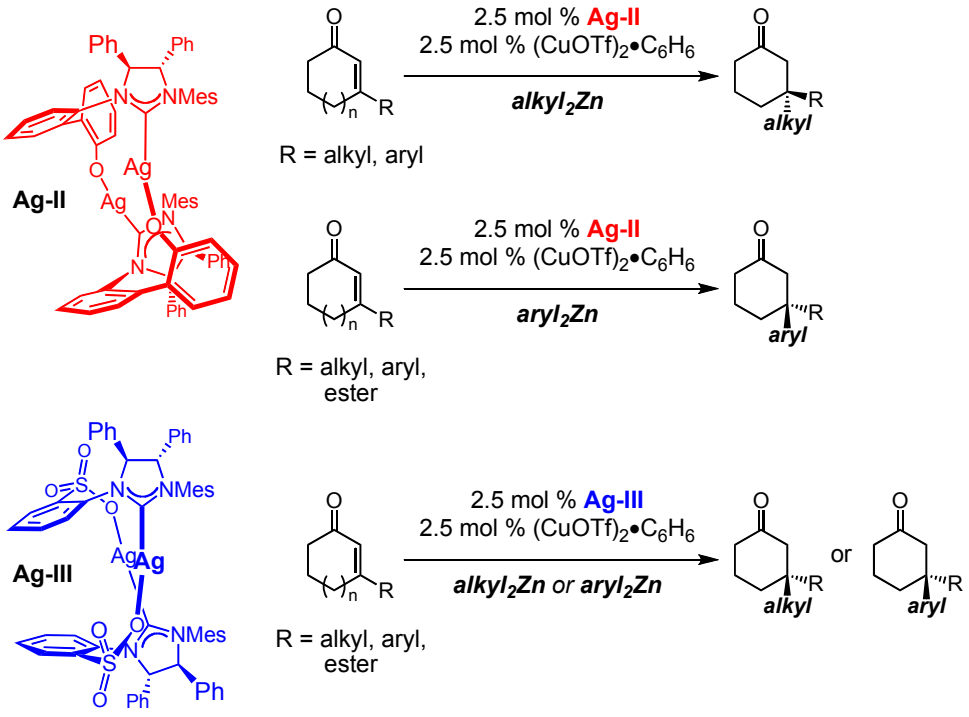


Figure 2.8: Proposal For Rate Enhancement with Bidentate NHC-Based Ligands

The major enantiomer generated for each substrate, dialkylzinc reagent and NHC ligand combination is provided in Scheme 2.34.[110] In all cases, addition of the nucleophile occurred from the front-face, except *dialkylzinc* addition to β-alkyl- or β-aryl substituted cyclic enones; in these examples addition proceeded from the back-face.

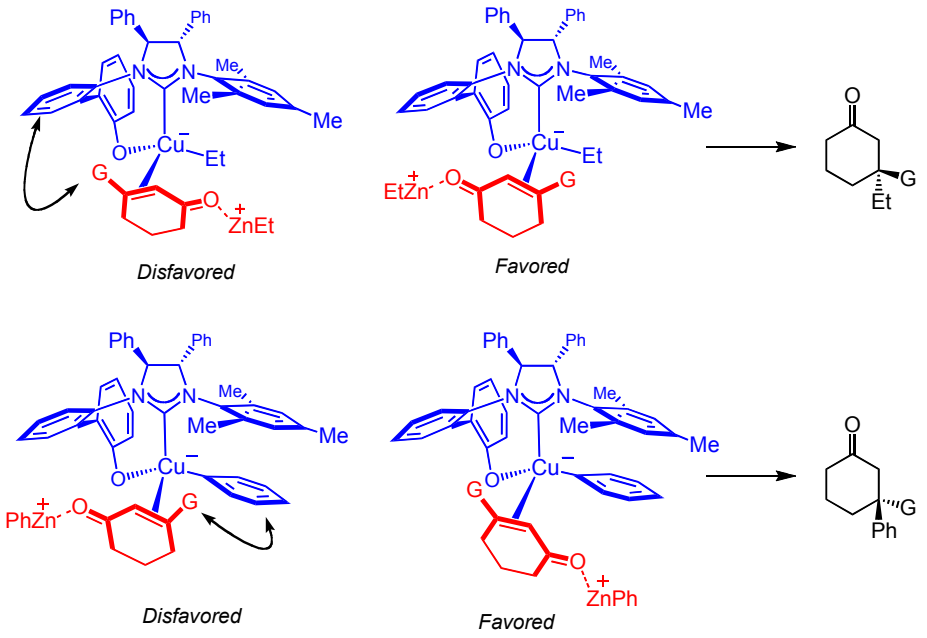
(110) See the Experimentals section for details.

Scheme 2.34: Major Enantiomer Generated for Various ACA Reactions



We have proposed models that account for the observed trends in selectivity (Scheme 2.35). With all models proposed, for steric considerations, it is likely that monomeric (vs. dimeric) Cu-NHC complexes are the active catalysts. For reactions of alkyl$_2$Zn reagents promoted by **Ag-II**, we propose that steric interaction between the β-substituent of the enone and the biphenyl moiety of the chiral ligand forces the substrate to complex to the back-face. In contrast, reactions of aryl$_2$Zn reagents promoted by **Ag-II**, the steric interaction between the aryl-Cu unit and the β-substituent of the enone may give rise to coordination to the front-face of the substrate.

Scheme 2.35: Proposed Working Models for Reactions with 2nd Generation NHC



In the case of NHC complexes of type **Ag-III**, the picture becomes more complicated as two potential modes of coordination of the sulfonate unit to Cu are possible. As illustrated in Figure 2.9, the sulfonate moiety was "*anti*" to the neighboring phenyl unit of the diamine backbone in **Ag-III**. The opposite scenario, however, was observed for Zn-NHC complex **Zn-III**; the phenyl and sulfonate groups were "*syn*" to each other.[111] Since the Zn-NHC complex **Zn-III** and our proposed models for Cu-NHC complexes are both monomeric it is likely that "*syn*" complexes were operative in the Cu-catalyzed process.

(111) Unpublished results of Yunmi Lee.

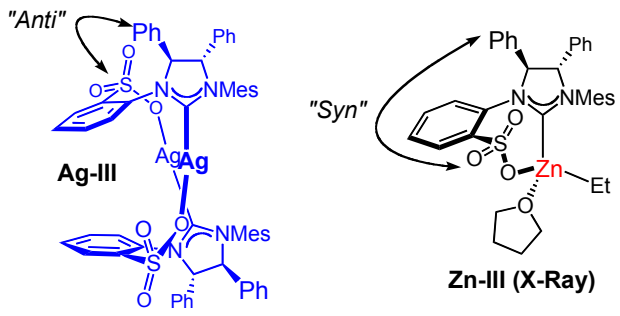
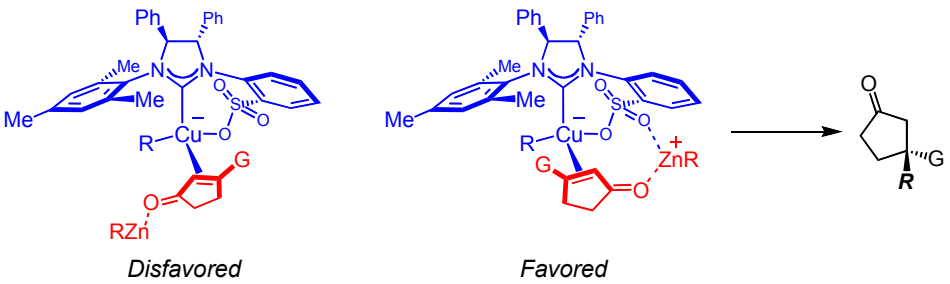


Figure 2.9: Syn/Anti Sulfonate Based NHC Complexes

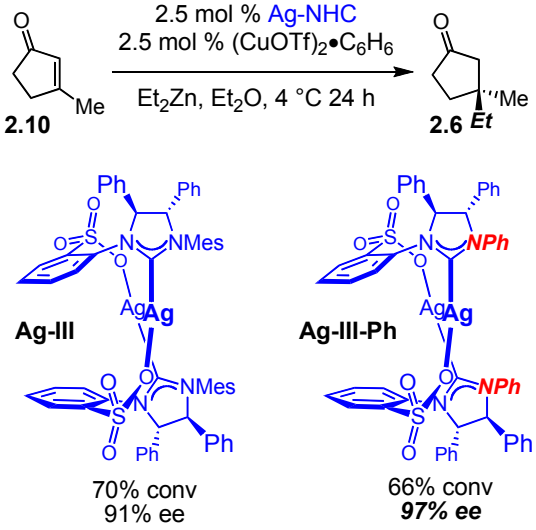
We propose that the favored substrate coordination to NHC-Cu complexes derived from **Ag-III** occurs with two-point binding (Scheme 2.36). To overcome the adverse steric interactions between the β-substituent of the enone and the mesityl unit in the favored complex, the substrate was activated internally by a Zn-bridge (vs. external activation as depicted in the disfavored complex), which could lower the energy of activation and thus lead to a more facile process. To test the proposed model for selectivity, we prepared **Ag-III-Ph** bearing a sterically less encumbered phenyl (vs. mesityl) unit (Scheme 2.37). It was our hope that the unfavorable interaction described above would be reduced. Indeed, catalytic ACA promoted by **Ag-III-Ph** provided **2.6** in improved ee (91% ee vs. 97% ee).[112]

Scheme 2.36: Proposed Working Models for Reactions with 3rd Generation NHC



(112) Unpublished results of Mikko Akiyama.

Scheme 2.37: Improved Selectivity for Cu-Catalyzed ACA Processes



While these models account for the observed major enantiomers generated, trends in selectivity are much more difficult to understand. For example, Ph_2Zn addition to cyclic unsaturated γ-keto ester **2.128** with **Ag-III** was non-selective (17% ee) while use of **Ag-II** led to a highly selective reaction (93% ee, Scheme 2.28). Based on the models presented in Scheme 2.35-2.36, we cannot account for this observation as well as related scenarios. High-level calculations will be needed to appreciate the subtle nuances of these complex processes.

2.5 *Conclusions*

Cu-catalyzed ACA reactions of dialkylzinc reagents promoted by Ag-NHC complexes **Ag-II** and **Ag-III** to a variety of β-substituted cyclic enones have been carried out. Development of these methods has allowed us to overcome many of the deficiencies associated with chiral peptide-based ligands in promoting ACA reactions to afford all-carbon quaternary stereogenic centers. For reactions involving unactivated six- and

seven-membered ring enones, **Ag-II** proved to be optimal. On the other hand, additions to unactivated five-membered ring enones, as well as cyclic unsaturated γ-keto esters, required the use of **Ag-III**. The practicality of ACA reactions promoted by NHC-based ligands has been demonstrated by carrying out the reaction on the bench top, in undistilled solvent and with commercial grade Cu-salts, as well as through the use of dialkylzinc reagents that have been prepared in situ. Mechanistic models that account for the observed enantiomer of products generated have been provided.

2.6 *Experimentals*

General. Infrared (IR) spectra were recorded on a Nicolet 210 spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm). High-resolution mass spectrometry were performed on a Micromass LCT ESI-MS (positive mode) at the Mass Spectrometry Facility, Boston College and at the University of Illinois Mass Spectrometry Laboratories

(Urbana, Illinois). Elemental microanalyses were performed at Robertson Microlit Laboratories (Madison, NJ). Enantiomer ratios were determined by chiral GLC analysis (Alltech Associated Chiraldex GTA column (30 m x 0.25 mm) and Betadex 120 column (30 m x 0.25 mm), and by chiral HPLC analysis (Chiral Technologies Chiralpak AS column, 25 cm x 0.46 cm) in comparison with authentic racemic materials. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Polarimeter.

Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 ^oC) and flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: toluene and benzene were purified through a copper oxide and alumina column; CH_2Cl_2 and Et_2O were purged with argon and purified by passage through two alumina columns. Tetrahydrofuran (Aldrich) and *t*-BuOMe (Acros, 99%) were purified by distillation from sodium benzophenone ketal immediately prior to use unless otherwise specified. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Doe & Ingalls) in air.

Reagents and Catalysts:

Ag-complexes Ag-I[113] **and Ag-II**[114] and **Ag-III** were prepared by previously reported methods.

(113) (a) "A Recyclable Chiral Ru Catalyst for Enantioselective Olefin Metathesis. Efficient Catalytic Asymmetric Ring-Opening/Cross Metathesis in Air," Van Veldhuizen, J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954-4955. (b) "Bidentate NHC-Based Chiral Ligands for Efficient Cu-Catalyzed Enantioselective Allylic Alkylations: Structure and Activity of an Air-Stable Chiral

Acetic acid was purchased from Fisher and used as received.

Acetic anhydride was purchased from Aldrich and used as received.

2,2'-Azobisisobutyronitrile was purchased from Aldrich and used as received.

Benzaldehyde was purchased from Aldrich and distilled from CaH_2 prior to use.

Racemic-2,2'-bis(diphenylphosphino)-1,1'-binapthyl (*rac*-binap) was purchased from Aldrich and used as received.

***t*-BuOH** was purchased from Aldrich and used as received.

Carbon disulfide was purchased from Aldrich and used as received.

Chloroform was purchased from Fisher and purified by distillation over $CaCl_2$ before use.

Chromium trioxide was purchased from Strem Inc. and used as received.

Copper (I) triflate benzene complex (2:1) (white solid) was prepared by previously reported methods.[115]

Copper (I) triflate toluene complex (2:1) (brown solid) was purchased from Aldrich (99.99%) and used as received.

Copper (I) oxide (99.9%) was purchased from Strem Inc. and used as received.

Dibutylzinc was purchased from Fluka (1M in heptane) and used as received.

Cu Complex," Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 1130-11131.

(114) "A Readily Available Chiral Ag-Based N-Heterocyclic Carbene Complex for Use in Efficient and Highly Enantioselective Ru-Catalyzed Olefin Metathesis and Cu-Catalyzed Allylic Alkylation Reactions," Van Veldhuizen, J. J.; Campbell, R. E.; Giudici, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877-6882.

(115) "Cationic Olefin Complexes of Copper(I). Structure and Bonding in Group Ib Metal-Olefin Complexes," R. G. Salomon, J. K. Kochi, *J. Am. Chem. Soc.* **1973**, *95*, 1889-1897.

Dicyclohexylcarbodiimide was purchased from Advanced Chem Tech and used as received.

Diethylzinc (neat) was purchased from Aldrich and used as received.

Diisopropylzinc (1M in toluene) was purchase from Aldrich and used as received.

Dimethylzinc (neat, 95%) was purchased from Strem Inc. and used as received.

Dioxane was distilled over Na prior to use.

Diphenylzinc (99%) was purchased from Strem Inc. (white solid) and used as received. Additionally, diphenylzinc can be prepared and purified (white solid) analogous to previously reported methods for the preparation of di-4-methoxyphenylzinc (see below for procedures) and used with similar levels of efficiency and selectivity. Diphenylzinc purchased from Aldrich (brown solid) was ineffective in the present Cu-catalyzed ACA.

4-Dimethylaminopyridine (DMAP) was purchased from Advanced Chem Tech and used as received.

***Di*-4-trifluoromethylphenyl zinc** was prepared by previously reported methods.[116]

Formaldehyde (37% aqueous solution) was purchased from Aldrich and used as received.

Iodomethane was purchased from Acros and used as received.

Lithium aluminum hydride (95%) was purchased from Strem Inc. and used as received.

$[(Me)_2CH(CH_2)_3]_2Zn$ was prepared by previously reported methods.[117]

Methyl 1-cyclopentene-1-carboxylate was purchased from Aldrich and used as received.

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(116) Chisholm, M. H.; Galluci, J. C.; Yin, H.; Zhen, H. *Inorg. Chem.* **2005**, *44*, 4777–4785.
(117) P. Knochel, R. Singer, *Chem. Rev.* **1993**, *93*, 2117-2188 and references cited therein.

Methyl-1-cyclohexene-1-carboxylate (**F**) was purchased from Aldrich and used as received.

Methyl-2-cyclohexenone was purchased from Aldrich and distilled prior to use.

Palladium(II) Acetate was purchased from Aldrich and used as received.

Phenyllithium (2.0 M in *n*-Bu_2O) was purchased from Acros and used as received.

Pyridine was purchased from Aldrich and purified by distillation over KOH before use.

Sodium *tert*-butoxide (98%) was purchased from Strem Inc. and used as received.

Sodium hydride was purchased from Strem Inc. and used as received.

Tri-*n*-butyltin hydride was purchased from Aldrich and used as received.

Triflic anhydride was prepared by distillation of triflic acid (Aldrich) over P_2O_5 (Aldrich).

Zinc (II) chloride (99.99%, ultradry), was purchased from Strem Inc. and used as received.

Chiral peptide based ligand 2.64 (Prepared in accordance with reported procedures).[118] **m.p.** 68-75 °C; **IR (neat):** 3370 (br s), 2974 (m), 2930 (m), 2867 (m), 1683 (s), 1652 (s), 1583 (m), 1501 (s), 1463 (s), 1381 (m), 1274 (m), 1224 (m), 1073 (m), 1029 (m), 809 (m), 733 (m), 626 (w), 513 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.76 (1H, d, *J* = 5.6 Hz), 7.72 (1H, t, *J* = 2.8 Hz), 7.63 (1H, t, *J* = 4.0 Hz), 7.14-7.01 (8H, m), 6.87-6.80 (2H, m), 4.00 (2H, dd, *J* = 4.0, 2.4 Hz), 3.90 (3H, m), 3.42 (1H, s), 3.38 (2H, dq, *J* = 7.2,

(118) "Modular Peptide-Based Phosphine Ligands in Asymmetric Catalysis: Efficient and Enantioselective Cu-Catalyzed Additions to Five-, Six-, and Seven-Membered Cyclic Enones," Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755-756.

2.4 Hz), 3.25 (2H, q, *J* = 7.2 Hz), 2.33 (6H, d, *J* = 6.0 Hz), 1.16 (3H, t, *J* = 7.2 Hz), 1.11 (3H, t, *J* = 7.2 Hz), 0.85 (9H, s); **^{13}C NMR: (100 MHz, $CDCl_3$):** δ 171.8, 167.2, 160.7, 160.5, 160.4, 140.7, 140.5, 138.8, 138.8, 135.2, 135.2, 134.1, 134.0, 133.8, 133.5, 133.4, 129.8, 129.7, 129.6, 129.5, 129.5, 118.0, 112.1, 112.1, 84.0, 55.7, 41.1, 40.9, 40.5, 35.3, 27.3, 21.5, 21.5, 14.3, 13.2; **Anal Calcd for $C_{34}H_{44}N_3O_3P$:** C, 71.18; H, 7.73; N, 7.15; Found C, 71.18; H, 7.73; N, 7.32; **Optical rotation:** $[\alpha]_D^{20}$ +30.6 (*c* 0.266, $CHCl_3$).

ν Representative experimental procedure for Cu-catalyzed conjugate addition of dialkylzinc reagents to γ-keto esters promoted by peptide based ligand 2.64: An oven-dried 13x100 mm test tube charged with **2.64** (8.6 mg, 0.015 mmol) and $(CuOTf)_2 \bullet C_6H_6$ (3.0 mg, 0.0060 mmol), weighed out under a N_2 atmosphere in a glove box, was sealed with a septum and parafilm and removed from the glove box. Toluene (1.0 mL) was added to afford an orange solution, and the resulting solution was allowed to cool to 0 °C. Diethylzinc (46.0 μL, 0.450 mmol) was added followed immediately by methyl 3-oxocyclopent-1-enecarboxylate (21.0 mg, 0.150 mmol) as a solution in toluene (500 μL). The mixture was allowed to stir at -30 °C for 24 h at which time the reaction was quenched by addition of saturated aqueous NH_4Cl (1 mL) then H_2O (1 mL). The aqueous layer was washed with EtOAc (2 x 2 mL). The combined organic layers were passed through a short plug of silica gel eluting with EtOAc and the filtrate was concentrated *in vacuo*. Purification by silica gel chromatography (30% diethyl ether/hexanes) yielded **2.57** as a clear oil (12.5 mg, 0.0735 mmol, 49.0%).

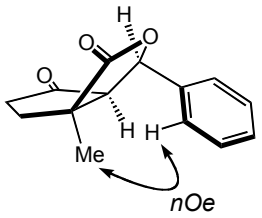
(*S*)-Methyl-1-ethyl-3-oxocyclopentanecarboxylate 2.57. For full characterization see below. **Optical rotation:** $[\alpha]_D^{20}$ +49.6 (*c* 0.286, $CHCl_3$) for an 81% ee sample. Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (β-dex column, 15 psi, 110 ^oC). T_{minor} = 44.458 min, T_{major} = 45.640 min.

(*S*)-*tert*-butyl 1-methyl-3-oxocyclopentanecarboxylate 2.66. For full characterization see below. **Optical rotation:** $[\alpha]_D^{20}$ +57.5 (*c* 0.893, $CHCl_3$) for an 94% ee sample. Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (β-dex column, 15 psi, 100 ^oC). T_{minor} = 65.151 min, T_{major} = 67.639 min.

(*S*)-*tert*-butyl 1-ethyl-3-oxocyclopentanecarboxylate 2.67. IR (neat): 2983 (m), 2940 (m), 2879 (w), 1747 (s), 1723 (s), 1472 (m), 1450 (m), 1380 (m), 1343 (m), 1252 (s), 1160 (s), 860 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.70 (1H, dd, *J* = 18, 1.2 Hz) 2.36-2.22 (3H, m), 2.02 (1H, d, *J* = 18.4 Hz), 1.86-1.77 (2H, m), 1.62-1.53 (1H, m), 1.42 (9H, s), 0.87 (3H, t, *J* = 7.2); **^{13}C NMR: (100 MHz, $CDCl_3$):** δ 217.5, 175.0, 81.3, 52.4, 47.2, 37.0,32.7, 31.4, 28.1, 10.0; **HRMS (EI^+):** Calcd for $C_{12}H_{21}O_3$ (M+H): 213.14907, Found: 213.14840; **Optical rotation:** $[\alpha]_D^{20}$ +63.7 (*c* 1.69, $CHCl_3$) for an 88% ee sample.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (β-dex column, 15 psi, 120 ^{o}C). T_{minor} = 36.180 min, T_{major} = 36.790 min.

6α-methyl-3-phenyl-tetrahydro-5*H*-cyclopenta[*c*]furan-1,4-dione (2.68). >30:1 mixture of diastereomers, relative configuration determined by *nOe* correlation**. IR (neat):** 3068 (w), 3026 (m), 2978 (w), 2930 (w), 2877 (w), 1785 (s), 1749 (s), 1504 (w), 1462 (m), 1385 (w), 1343 (w), 1289 (m), 1265 (m), 1224 (m), 1170 (m), 1170 (s), 1062 (m), 1021 (m), 746 (m), 704 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.41-7.29 (5H, m), 5.53 (1H, d, *J* = 2.8 Hz), 2.76 (1H, d, *J* = 2.8 Hz), 2.57-2.49 (2H, m), 2.43-2.32 (1H, m), 2.01-1.93 (1H, m), 1.32 (3H, s); **^{13}C NMR: (100 MHz, $CDCl_3$):** δ 216.0, 180.7, 139.4, 129.1, 128.5, 124.6, 79.6, 62.4, 48.3, 37.8, 32.7, 23.3; **HRMS:** Calcd for $C_{14}H_{14}O_3$ 230.0943; Found 230.0946; **Optical rotation:** $[\alpha]_D^{20}$ +75.5 (*c* 0.173, $CHCl_3$) for an 91% ee sample. Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (Chiraldex GTA column, 15 psi, 140 ^{o}C). T_{major} = 86.7 min, T_{minor} = 96.8 min.



ν Clasien Condensation Product 2.63: The side product characterized was isolated from of ACA of Me_2Zn to **2.56**. For clarity the side product derived from ACA of Et_2Zn to **2.56** was presented in the text.

Two diastereomers were isolated. A) **IR (neat):** 2952 (br w), 2928 (br w), 1771 (s), 1743 (s), 1720 (s), 1437 (w), 1310 (m), 1272 (m), 1254 (m), 1203 (m), 1163 (m), 942 (m), 923 (m), 750 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.58 (1H, dt, *J* = 2.0, 0.8 Hz), 3.79 (3H, s), 2.81-2.73 (1H, m), 2.67-2.43 (4H, m), 2.32-2.22 (1H, m), 2.04-1.98 (1H, m), 1.88 (1H, ddd, *J* = 12.8, 11.6, 7.6 Hz), 1.57 (3H, s); **HRMS:** Calcd for $C_{14}H_{17}O_5$ 265.10760; Found 265.10761.

B) **IR (neat):** 2953 (br w), 1771 (s), 1744 (s), 1722 (s), 1438 (w), 1305 (m), 1253 (m), 1226 (m), 1192 (m), 1134 (m), 1159 (m), 1054 (w), 950 (w), 751 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.39 (1H, t, *J* = 2.0 Hz), 3.78 (3H, s), 2.86-2.78 (1H, m), 2.71-2.63 (2H, m), 2.58-2.38 (4H, m), 2.34-2.24 (2H, m), 1.92 (1H, ddd, *J* = 13.2, 12.0, 8.4 Hz), 1.56 (3H, s); **HRMS:** Calcd for $C_{14}H_{17}O_5$ 265.10760; Found 265.10629.

ν Preparation of unactivated enones: α,β-Unsaturated carbonyls were either commercially available or prepared according to published procedures.[119]

ν Representative experimental procedure for Cu-catalyzed conjugate addition of $(alkyl)_2Zn$ reagents to unactivated cyclic enones promoted by Ag-II: An oven-dried 13x100 mm test tube charged with chiral **Ag-II** (4.5 mg, 0.0036 mmol), $(CuOTf)_2 \bullet C_6H_6$ (1.8 mg, 0.0036 mmol) and 3-methyl-2-cyclohexenone (16 mg, 0.14 mmol) was weighed out under an N_2 atmosphere in a glove box. The test tube was sealed with a septum, wrapped with parafilm before removal from the glove box. Diethyl ether (1.0 mL) was added at 22 °C; the resulting solution was allowed to stir for 10 min. Diethylzinc (45 μL, 0.43 mmol) was slowly added to the mixture at –78 °C; during the addition of Et_2Zn the reaction became dark brown. After 48 h at –30 °C, the reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (1 mL) and then immediately H_2O (1 mL). The mixture was washed with Et_2O (3x1 mL) and the combined organic layers were passed through a short plug (4 cm x 1 cm) of silica gel eluted with Et_2O. The volatiles were removed in vacuo and the resulting dark brown oil was purified by silica gel column chromatography (hexanes/Et_2O:10/1) to afford 19.4 mg (0.138 mmol, 95.1% yield) of **2.35** as a colorless oil. **Important note:** To ensure high

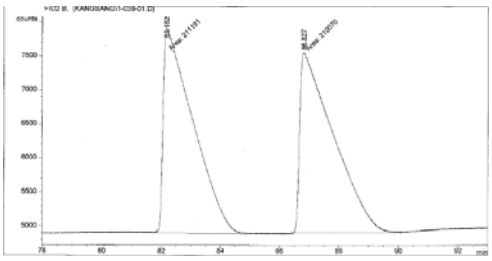
(119) (a) "A Copper-Free Palladium Catalyzed Cross Coupling Reaction of Vinyl Tosylates with Terminal Acetylenes," Fu, X.; Zhang, S.; Yin, J.; Schumacher, D. P. *Tetrahedron Lett*. **2002**, *43*, 6673–6676. (b) "Direct Oxidation of Tertiary Allylic Alcohols. A Simple and Effective Method for Alkylative Carbonyl Transposition," Dauben, W. G.; Michno, D. M. *J. Org. Chem*. **1977**, *42*, 682–685. (c) "Intramolecular Addition Reactions of Carbonyl Ylides formed During Photocyclization of Aryl Vinyl Ethers," Dittami, J. P.; Nie, X. Y.; Nie, H.; Ramanathan, H.; Breining, S. *J. Org. Chem*. **1991**, *56*, 5572–5578.

efficiency and enantioselectivity, reactions must be set up in exactly the order described above.

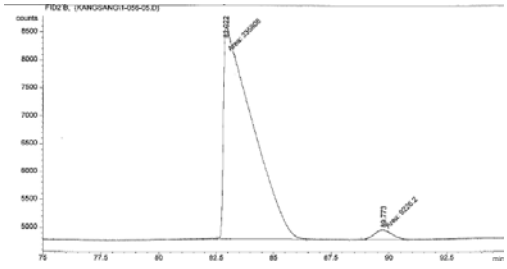
■ **Representative procedure for Cu-Catalyzed conjugate addition of Et_2Zn to unactivated enones *set up on the bench top and performed in undistilled diethyl ether*:** A 13 x 100 mm test tube charged with **Ag-II** (4.5 mg, 0.0036 mmol), $(CuOTf)_2 \bullet C_6H_6$ (1.8 mg, 0.0036 mmol), and 3-methyl-2-cyclohexenone (16 mg, 0.14 mmol) weighed out on the bench top in air, was sealed with a septum, wrapped with parafilm, and purged with N_2. Undistilled Et_2O (1.0 mL) was added at 22 °C; the resulting solution was allowed to stir for 10 min. Diethylzinc (45 μL, 0.43 mmol) was slowly added to the mixture at –78 °C; during the addition of diethylzinc the reaction became dark brown. After 48 h at –30 °C, the reaction was quenched by the addition of a saturated solution of aqueous ammonium chloride (1.0 mL) and then immediately H_2O (1.0 mL). The mixture was washed with Et_2O (3x1 mL) and passed through a short plug of silica eluted with the same solvent. The volatiles were removed in vacuo to afford a light yellow oil, which was purified by silica gel column chromatography (hexanes/Et_2O: 10/1) to afford 18.2 mg (0.130 mmol, 95.1% yield) of cyclic ketone **2.35** as a colorless oil. **Important note:** To ensure high efficiency and enantioselectivity reactions must be set up in exactly the order described above.

(*R*)-(+)-3-Ethyl-3-methylcyclohexanone (2.35). IR (neat): 2962 (s), 2936 (s), 2879 (m), 2855 (w), 1715 (s), 1464 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.27 (2H, dd, *J* = 6.8, 6.8 Hz), 2.18 (1H, d, *J* = 13.6 Hz), 2.09 (1H, d, *J* = 13.6 Hz), 1.90-1.83 (2H, m), 1.66-1.50 (2H, m), 1.35-1.29 (2H, m), 0.90 (3H, s), 0.84 (3H, t, *J* = 7.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 212.4, 53.4, 41.0, 38.7, 35.4, 34.0, 24.4, 22.1, 7.7; Anal Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50; Found C, 76.86; H, 11.25; **HRMS Calcd for $C_9H_{16}O$ (EI^+):** 140.1201, Found: 140.1196; **Optical rotation:** $[\alpha]_D^{20}$ +8.0 (*c* 1.0, $CHCl_3$) for an 87% ee sample.

Optical purity was determined by chiral GLC analysis in comparison with authentic racemic material (95% ee shown below; *β*-dex chiral column, 80 °C, 15 psi).



Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	82.182	MM	1.1595	2.11191e5	3035.64307	50.13298
2	86.827	MM	1.3123	2.10070e5	2667.89673	49.86702

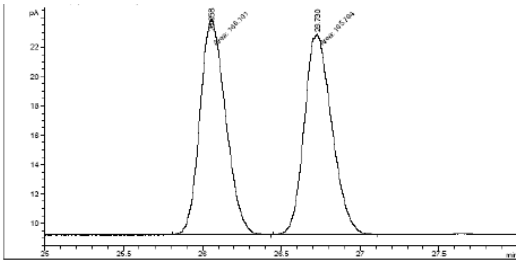


Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	82.922	MM	1.4721	3.35808e5	3801.86841	97.32600
2	89.773	MM	0.8482	9226.20117	181.28061	2.67400

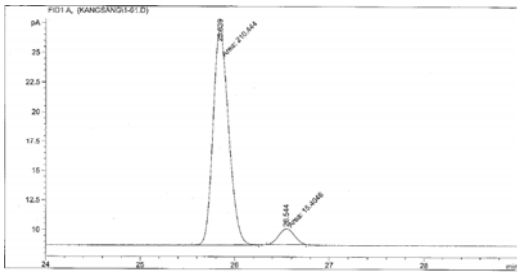
(*R*)-3-Butyl-3-methylcyclohexanone (2.97). IR (neat): 2957 (s), 2931 (s), 2870 (m), 2860 (m), 1715 (s), 1467 (w), 1457 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.26 (2H, dd, *J* = 7.2, 7.2 Hz), 2.17 (1H, d, *J* = 13.6 Hz), 2.09 (1H, d, *J* = 13.6 Hz), 1.88-1.81 (2H, m), 1.65-1.48 (2H, m), 1.29-1.17 (6H, m), 0.90 (6H, m); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 212.7, 54.0, 41.4, 41.2, 38.7, 36.0, 25.7, 25.3, 23.5, 22.3, 14.2; **HRMS (EI^+):** Calcd for

$C_{11}H_{20}O$ (M+H): 169.1592, Found: 169.1593; **Optical rotation:** $[\alpha]_D^{20}$ +1.15 (*c* 1.00, $CHCl_3$) for an 86% ee sample.

Optical purity was determined by chiral GLC analysis in comparison with authentic racemic material (86% ee sample below; *β*-dex column, 120 °C, 15 psi).



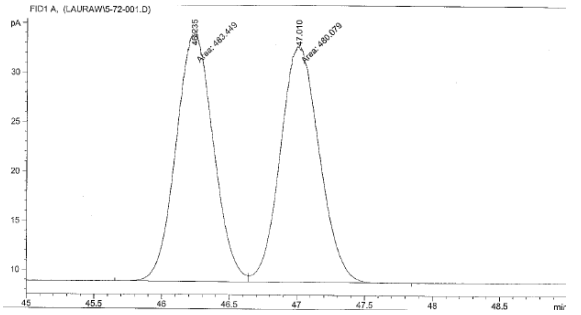
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	26.058	MM	0.1889	166.10118	14.65485	50.05075
2	26.730	MM	0.2025	165.76436	13.64158	49.94925



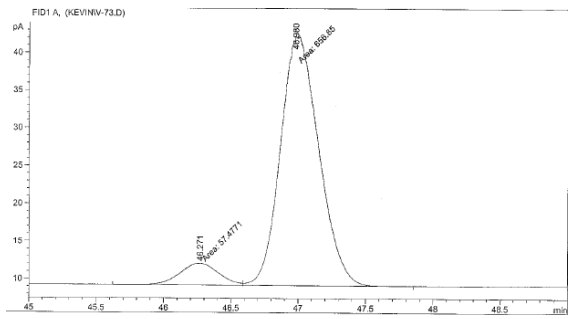
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	25.839	MM	0.1926	210.44351	18.20629	93.17922
2	26.544	MM	0.1933	15.40460	1.32817	6.82078

(*R*)-3-Ethyl-3-(4-pentenyl)cyclohexanone (2.98). IR (neat): 3087 (w), 2936 (s), 1721 (s), 1646 (w), 1463 (m), 1419 (m), 1388 (w), 1350 (w), 1318 (w), 1230 (w), 1092 (w), 1004 (m), 903 (m) cm^{-1}; **^{1}H NMR (400 MHz. $CDCl_3$):** δ 5.57 (1H, dddd, *J* = 17.2, 10.4, 6.8, 6.8 Hz), 5.00-4.91 (2H, m), 2.25 (2H, t, *J* = 6.8 Hz), 2.12 (2H, s), 2.02-1.96 (2H, m), 1.84-1.78 (2H, m), 1.57-1.54 (2H, m), 1.31-1.18 (6H, m), 0.76 (3H, t, *J* = 7.2 Hz); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 212.8, 138.8, 114.9, 52.1, 41.3, 41.1, 36.1, 34.5, 33.6, 29.7, 22.4, 21.9, 7.6; **HRMS**: Calcd for $C_{13}H_{22}O$: 194.1671, Found: 194.1675; **Optical rotation:** $[\alpha]_D^{20}$ +4.87 (*c* 1.29, $CHCl_3$) for an 82% ee sample.

Optical purity was determined by chiral GLC analysis in comparison with authentic racemic material (84% ee sample below; conditions: *β*-dex column, 130 °C, 15 psi).



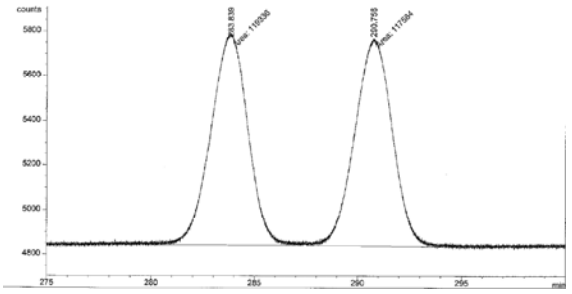
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	46.235	MF	0.3189	483.44894	25.26414	50.17489
2	47.010	FM	0.3335	480.07880	23.99061	49.82511



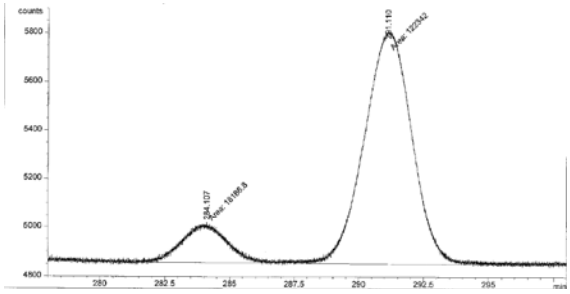
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	46.271	MF	0.3316	57.47711	2.88916	8.04633
2	46.980	FM	0.3302	656.85004	33.15128	91.95367

(*S*)-3-Ethyl-3-(2-phenyl ethynyl)cyclohexanone (2.100). **IR (neat):** 2965 (m), 2926 (m), 2874 (w), 2853 (w), 2359 (w), 2338 (w), 1716 (s), 1597 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37-7.33 (2H, m), 7.27-7.23 (3H, m), 2.59 (1H, ddd, *J* = 14.0, 2.0, 2.0 Hz), 2.44-2.38 (1H, m), 2.30-2.10 (3H, m), 2.06-1.96 (2H, m), 1.69-1.58 (3H, m), 1.07 (3H, t, *J* = 7.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 209.6, 131.9, 128.3, 128.1, 123.5, 92.1, 85.1, 52.6, 41.5, 41.2, 35.9, 35.0, 23.0, 9.1; **HRMS (EI^+):** Calcd for $C_{16}H_{18}O$: 226.1358, Found: 226.1363; **Optical rotation:** $[\alpha]_D^{20}$ +39.9 (*c* 1.00, $CHCl_3$) for a 74% ee sample.

Optical purity was determined by chiral GLC analysis in comparison with authentic racemic material. (74% ee sample below; conditions: *β*-dex column, 140 °C, 15 psi).

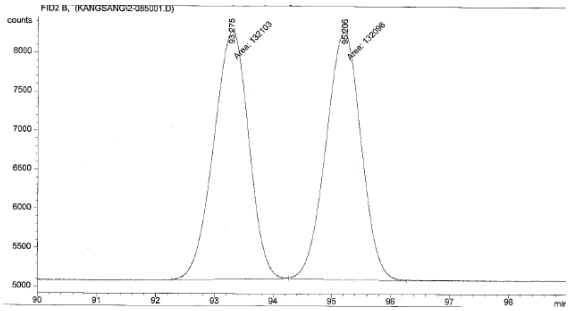


Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	283.839	MM	2.0926	1.19336e5	950.48395	50.36984
2	290.756	MM	2.0956	1.17584e5	935.14319	49.63016

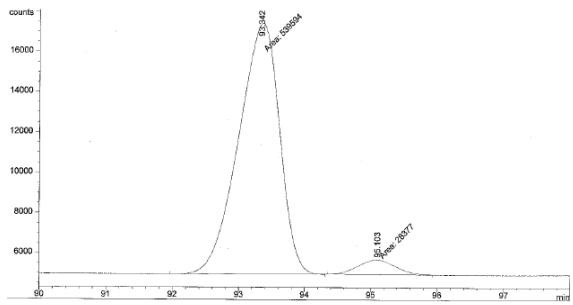


Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	284.107	MM	1.8360	1.81868e4	165.09117	12.94168
2	291.110	MM	2.1275	1.22342e5	958.42578	87.05832

(*S*)-3-Ethyl-3-phenylcyclohexanone (2.99): For full characterization see below. Optical purity was determined by chiral GLC analysis in comparison with authentic racemic material. (90% ee sample below; conditions: β-dex column, 140 °C, 15 psi).



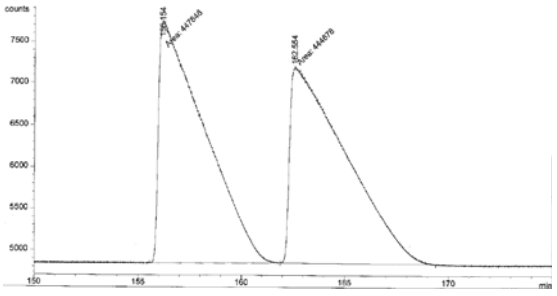
Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	93.275	MM	0.6928	1.32103e5	3178.05493	50.00130
2	95.206	MM	0.6941	1.32096e5	3172.08765	49.99870



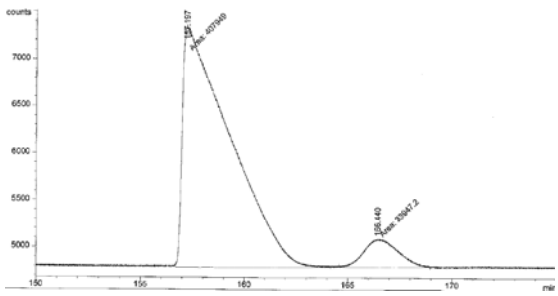
Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	93.342	MM	0.7211	5.39593e5	1.24716e4	95.00379
2	95.103	MM	0.6519	2.83770e4	725.45056	4.99621

(*R*)-3-Ethyl-3-methylcycloheptanone (ent-**2.5). IR (neat):** 2964 (m), 2929 (s), 2882 (w), 2861 (w), 1697 (s), 1464 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.51 (1H, d, J = 12.0 Hz), 2.41-2.37 (2H, m), 2.35 (1H, d, J = 12.0 Hz), 1.78-1.47 (6H, m), 1.34-1.23 (2H, m), 0.86 (3H, s), 0.83 (3H, t, J = 7.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 214.4, 54.2,

44.1, 42.2, 35.4, 35.0, 25.5, 24.8, 24.3, 8.0; **HRMS (EI^+):** Calcd for $C_{10}H_{18}O$: 154.1358, Found: 154.1356; **Optical rotation:** $[\alpha]_D^{20}$ +17.1 (*c* 1.00, $CHCl_3$) for an 85% ee sample. Optical purity was determined by chiral GLC analysis in comparison with authentic racemic material (85% ee sample below; conditions: β-dex column, 80 °C, 15 psi).



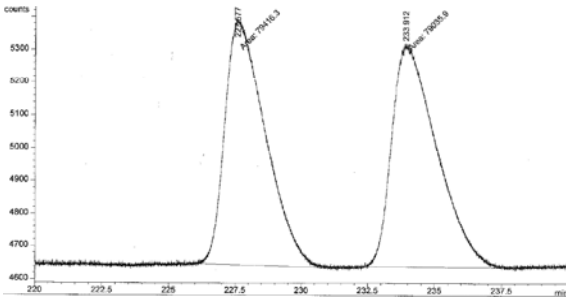
Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	156.154	MM	2.5541	4.47848e5	2922.39160	50.17758
2	162.554	MM	3.1335	4.44678e5	2365.15771	49.82242



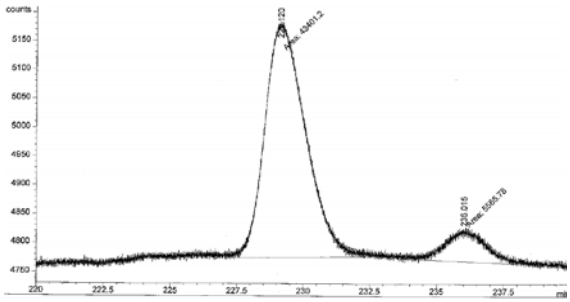
Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	157.197	MM	2.6336	4.07949e5	2581.69385	92.31784
2	166.440	MM	1.8549	3.39472e4	305.02258	7.68216

(*R*)-3-Butyl-3-methylcycloheptanone (2.101). IR (neat): 2958 (s), 2934 (s), 2871 (m), 2859 (m), 1701 (s), 1461 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.51 (1H, d, *J* = 12.4 Hz), 2.41-2.35 (3H, m), 1.77-1.57 (5H, m), 1.52-1.47 (1H, m), 1.23-1.17 (6H, m), 0.90-0.86 (6H, m); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 214.5, 55.0, 44.1, 42.7, 42.4, 35.3, 26.2, 25.8, 24.8, 24.3, 23.5, 14.2; **Anal Calcd for $C_{12}H_{22}O$:** C, 79.06; H, 12.16; Found C, 78.89; H, 12.14; **HRMS (EI^+):** Calcd for $C_{12}H_{22}O$: 182.1671, Found: 182.1668. Optical rotation: $[\alpha]_D^{20}$ +10.0° (c = 1.00, $CHCl_3$) for a 77% ee sample.

Optical purity was determined by chiral GLC analysis in comparison with authentic racemic material (77% ee sample below; conditions: *β*-dex column, 90 °C, 15 psi).



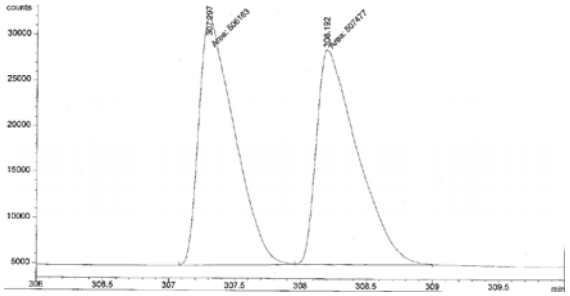
Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	227.577	MM	1.7676	7.94163e4	748.79749	50.12005
2	233.912	MM	1.9260	7.90359e4	683.92627	49.87995



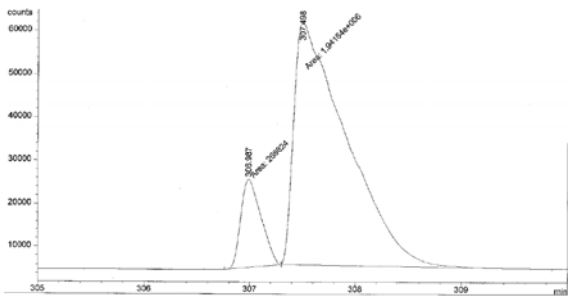
Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	229.120	MM	1.7526	4.34012e4	412.74313	88.63362
2	236.015	MM	1.6311	5565.77881	56.87172	11.36638

(*S*)-3-Butyl-3-ethylcycloheptanone (2.102). IR (neat): 2958 (s), 2927 (s), 2871 (m), 2861 (m), 1697 (m), 1458 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.43 (2H, s), 2.39 (2H, t, *J* = 6.2 Hz), 1.77-1.72 (2H, m), 1.64-1.60 (2H, m), 1.57-1.53 (2H, m), 1.34-1.13 (8H, m), 0.88 (3H, t, *J* = 7.0 Hz), 0.79 (3H, t, *J* = 7.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 214.8, 53.5, 44.1, 40.1, 37.7, 37.4, 30.7, 25.2, 24.4, 24.4, 23.6, 14.2, 7.6; **HRMS (EI^+):** Calcd for $C_{13}H_{24}O$: 196.1827, Found: 196.1827; **Optical rotation:** $[\alpha]_D^{20}$ +5.98 (c 1.00, $CHCl_3$) for a 76% ee sample.

Optical purity was determined by chiral GLC analysis in comparison with authentic racemic material (76% ee sample below; conditions: *β*-dex column, 90 °C (300 min), 20 °C/min to 140°C (10 min), 15 psi).



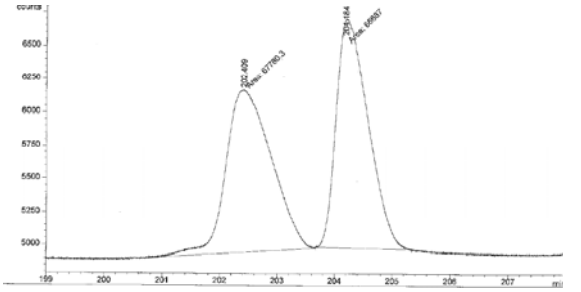
Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	307.297	MM	0.3128	5.06163e5	2.69736e4	49.93517
2	308.192	MM	0.3589	5.07477e5	2.35658e4	50.06483



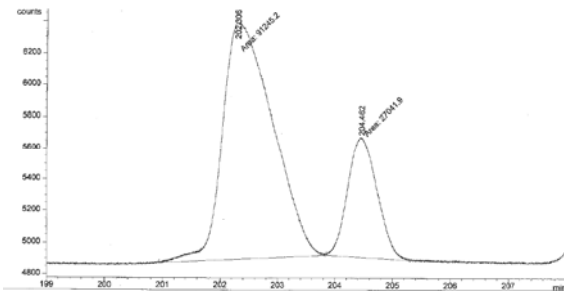
Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	306.987	MM	0.2213	2.69824e5	2.03245e4	12.20116
2	307.498	MM	0.5791	1.94164e6	5.58768e4	87.79884

(*R*)-3-Ethyl-3-methylcyclooctanone. IR (neat): 2955 (m), 2924 (s), 2875 (w), 2852 (w), 1695 (s), 1470 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.39 (1H, d, *J* = 10.8 Hz), 2.29 (2H, ddd, *J* = 8.0, 4.0, 4.0 Hz), 2.17 (1H, d, *J* = 10.8 Hz), 1.95-1.87 (2H, m), 1.53-1.47 (2H, m), 1.42-1.25 (6H, m), 0.91 (3H, s), 0.84 (3H, t, *J* = 7.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 215.5, 48.8, 45.5, 39.0, 37.0, 34.7, 29.1, 25.6, 22.0, 20.3, 8.3; **HRMS (EI^+):** Calcd for $C_{11}H_{20}O$: 168.1514, Found: 168.1511; **Optical rotation:** $[\alpha]_D^{20}$ +9.28 (c 0.500, $CHCl_3$) for a 54% ee sample.

Optical purity was determined by chiral GLC analysis in comparison with authentic racemic material (54% ee sample below; conditions: *β*-dex column, 90 °C (300 min), 20 °C/min to 140°C (10 min), 15 psi).



Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	202.409	MM	0.9227	6.77803e4	1224.28467	50.40651
2	204.184	MM	0.6421	6.66870e4	1730.88135	49.59349



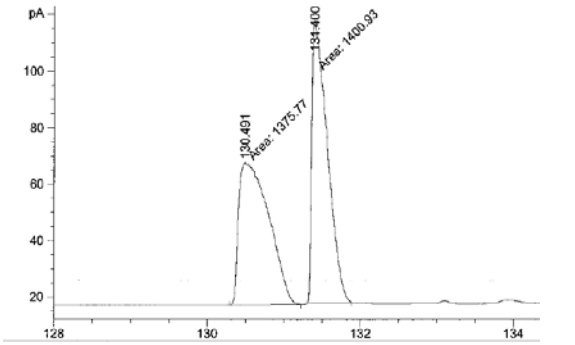
Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	202.306	MM	1.0147	9.12452e4	1498.75061	77.13878
2	204.462	MM	0.5898	2.70419e4	764.11066	22.86122

ν Representative experimental procedure for Cu-catalyzed conjugate addition of (aryl)$_2$Zn reagents. An oven-dried 13x100 mm test tube was charged with **Ag-II** (5.6 mg, 0.0045 mmol), $(CuOTf)_2 \cdot C_6H_6$ (2.7 mg, 0.0045 mmol), 3-methyl-2-cyclohexenone (20 mg, 0.18 mmol), and Ph_2Zn (120 mg, 0.55 mmol), which were weighed out under a N_2 atmosphere in a glove box (in the precise order mentioned above). The test tube was sealed with a septum, wrapped with parafilm, and the reaction vessel was removed from the glove box. Diethyl ether (1.0 mL) was slowly added to the mixture in a dropwise manner (syringe) at –78 °C. After 48 h at –30 °C, the reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (1.0 mL) and then immediately H_2O (1.0 mL). The mixture was washed with Et_2O (3 x 1 mL) and the combined organic layers were passed through a short plug of silica eluted with Et_2O. The volatiles were removed in vacuo and the resulting mixture was purified by silica gel column chromatography (hexanes/Et_2O: 10/1) to afford 32.5 mg (0.173 mmol, 95.0% yield) of cyclic ketone ent-**2.7** as a colorless oil. **Important note:** To ensure high

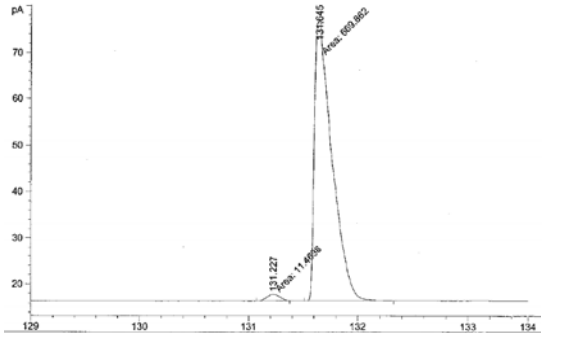
efficiency and enantioselectivity, reactions must be set up in exactly the order described above.

(*S*)-3-Methyl-3-phenylcyclohexanone (ent-**2.7). IR (neat):** 3087 (w), 3058 (w), 3024 (w), 3022 (w), 2962 (s), 2937 (s), 2870 (m), 2357 (w), 2332 (w), 1715 (s), 1602 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35-7.30 (4H, m), 7.26-7.18 (1H, m), 2.89 (1H, d, *J* = 14.4 Hz), 2.44 (1H, d, *J* = 14.4 Hz), 2.31 (2H, t, *J* = 6.8 Hz), 2.22-2.16 (1H, m), 1.96-1.83 (2H, m), 1.72-1.61 (1H, m), 1.33 (3H, s); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 211.6, 147.5, 128.6, 126.3, 125.7, 53.2, 42.9, 40.9, 38.0, 29.9, 22.1; Anal Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57; Found C, 82.67; H, 8.28; **HRMS (EI^+):** Calcd for $C_{13}H_{16}O$: 188.1201, Found: 188.1199; **Optical rotation:** $[\alpha]_D^{20}$ +70.2 (*c* 1.00, $CHCl_3$) for a 97% ee sample.

Optical purity was determined by chiral GLC analysis in comparison with authentic racemic material (97% ee sample below; conditions: CDGTA column, 95 °C (70 min), 0.5 °C/min to 110°C (30 min), 20°C/min to 140°C (20 min), 15 psi).



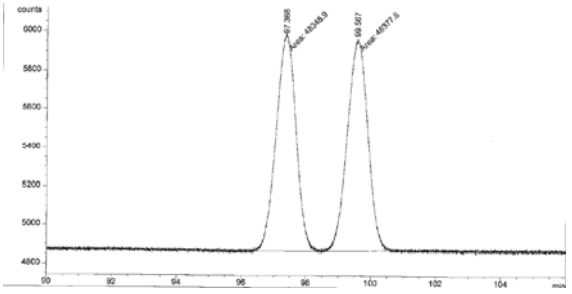
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	130.491	MM	0.4514	1375.76965	50.79977	49.54694
2	131.400	MM	0.2332	1400.93005	100.12084	50.45306



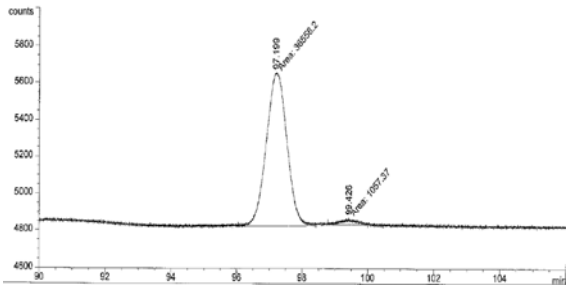
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	131.227	MM	0.1345	11.46359	1.42041	1.68254
2	131.645	MM	0.1836	669.86230	60.79257	98.31746

(*S*)-3-Ethyl-3-phenylcyclohexanone (2.99). IR (neat): 3089 (w), 3058 (w), 3031 (w), 3024 (w) 2962 (s), 2934 (s), 2877 (m), 2355 (w), 2332 (w), 1715 (s), 1601 (w), 1498 (m), 1460 (m), 1445 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32-7.27 (2H, m), 7.25-7.22 (2H, m), 7.20-7.15 (1H, m), 2.90 (1H, d, *J* = 14.4 Hz), 2.40 (1H, d, *J* = 14.4 Hz), 2.30-2.26 (2H, m), 2.19-2.13 (1H, m), 2.00-1.93 (1H, m), 1.84-1.54 (4H, m), 0.58 (3H, t, *J* = 7.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 211.6, 145.0, 128.6, 126.7, 126.2, 50.7, 46.6, 41.2, 36.4, 35.8, 21.7, 8.1; **HRMS (EI^+):** Calcd for $C_{14}H_{18}O$: 202.1358, Found: 202.1362. **Optical rotation:** $[\alpha]_D^{20}$ +63.8 (*c* = 1.00, $CHCl_3$) for a 94% ee sample.

Optical purity was determined by chiral GLC analysis in comparison with authentic racemic material (94% ee sample below; conditions: *β*-dex column, 140 °C, 15 psi).



Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	97.368	MM	0.7094	4.83489e4	1135.85632	49.98504
2	99.567	MM	0.7347	4.83778e4	1097.49817	50.01496

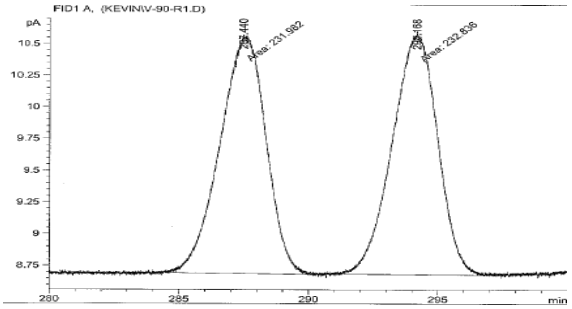


Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	97.199	MM	0.7261	3.65582e4	839.13165	97.18902
2	99.426	MM	0.4772	1057.36670	37.46599	2.81098

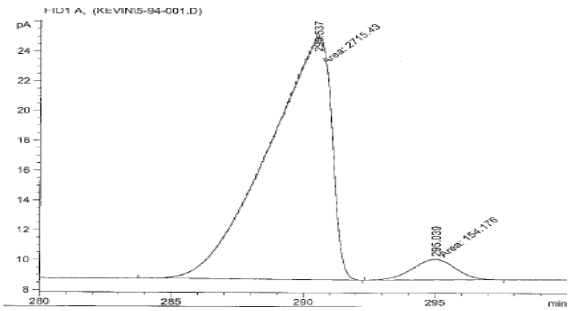
(*S*)-3-(4-pentenyl)-3-phenylcyclohexanone (2.103). IR (neat): 2936 (s), 2873 (m), 1709 (s), 1645 (m), 1438 (m), 1332 (m), 1242 (m), 996 (w), 918 (m), 762 (m), 711 (s), 667 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32-7.26 (2H, m), 7.25-7.22 (2H, m), 7.20-7.15 (1H, m), 5.63 (1H, dddd, *J* = 17.2, 10.4, 6.8, 6.8 Hz), 4.91-4.85 (2H, m), 2.91

(1H, d, J = 14.0 Hz), 2.42 (1H, d, J = 14.0 Hz), 2.26-2.26 (2H, m), 2.19-2.00 (1H, m), 2.00-1.51 (7H, m), 1.20-1.09 (1H, m), 0.99-0.88 (1H, m); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 211.7, 145.3, 138.6, 128.7, 126.6, 126.3, 114.9, 51.3, 46.3, 42.8, 41.2, 36.8, 34.1, 22.9, 21.7. **HRMS:** Calcd for $C_{17}H_{22}O$: 242.1671, Found: 242.1676; **Optical rotation:** $[\alpha]_D^{20}$ +45.2 (c 1.97, $CHCl_3$) for an 89% ee sample.

Optical purity was determined by chiral GLC analysis in comparison with authentic racemic material (89% ee sample below; conditions: β-dex column, 120 °C, 15 psi).



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	287.440	MM	2.0577	231.98180	1.87901	49.90811
2	294.168	MM	2.0192	232.83606	1.92182	50.09189

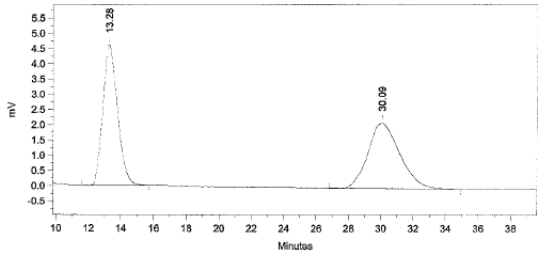


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	290.537	MM	2.7365	2715.43164	16.53853	94.62728
2	295.039	MM	1.8292	154.17613	1.40478	5.37272

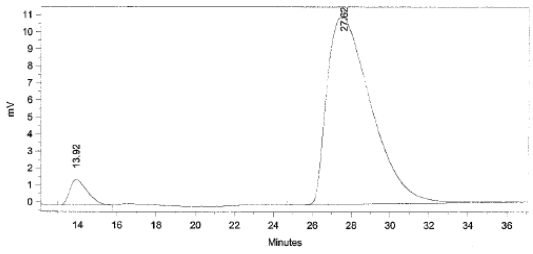
(*S*)-3-(4-methoxyphenyl)-3-methylcyclohexanone. The general procedure described on page 7 was followed, except that toluene was used as the solvent. **IR (neat):** 2964 (s), 2880 (m), 1712 (s), 1611 (m), 1516 (s), 1455 (m), 1309 (m), 1259 (s), 1186 (m), 1041 (m), 840 (m) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.21 (2H, dt, J = 5.6, 3.6 Hz), 6.84 (2H, dt, J = 5.6, 3.6 Hz), 3.37 (3H, s), 2.83 (1H, d, J = 14.4 Hz), 2.40 (1H, d, J = 14.4 Hz), 2.85 (2H, t, J = 6.8 Hz), 2.17-2.11 (1H, m), 1.91-1.80 (2H, m), 1.69-1.59 (1H, m), 1.28 (3H, s). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 200.7, 158.0, 139.7, 126.9, 114.0, 55.4,

53.5, 42.5, 41.5, 38.3, 30.3, 22.2. **HRMS:** Calcd for $C_{14}H_{18}O$: 218.1307, Found: 218.1298; **Optical Rotation:** $[\alpha]_D^{20}$ +51.7 (*c* = 0.960, $CHCl_3$) for a 90% ee sample.

Optical purity was determined by chiral HPLC analysis in comparison with authentic racemic material (90% sample below; conditions: chiralpak AS column (25 cm x 0.46 cm), 95/5 hexanes/*i*-PrOH, 1.0 mL/min, 254 nm).



PK#	Ret Time	Name	Amount	Amount%	Area	Area%
1	13.282		0.0000	0.000	288783.6	49.612
2	30.087		0.0000	0.000	293300.6	50.388

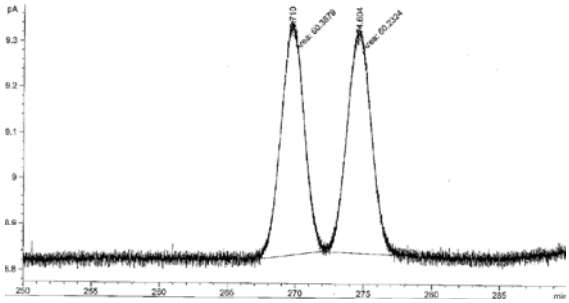


PK#	Ret Time	Name	Amount	Amount%	Area	Area%
1	13.922		0.0000	0.000	92177.0	5.049
2	27.619		0.0000	0.000	1733598.0	94.951

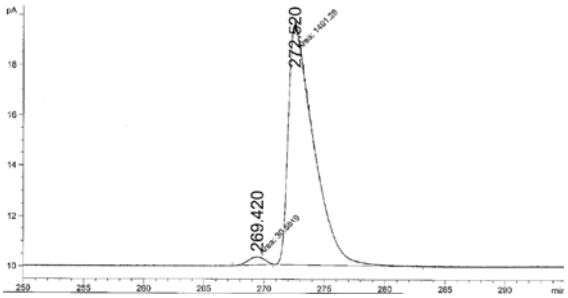
(*S*)-3-Methyl-3-phenylcycloheptanone (2.104). IR (neat): 3088 (w), 3056 (m), 3032 (m), 3022 (m) 2931 (s), 2862 (s), 1949 (w), 1877 (w), 1805 (w), 1696 (s), 1599 (m), 1497 (s), 1460 (s), 1444 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33-7.30 (4H, m), 7.22-7.17 (1H, m), 3.21 (1H, d, *J* = 14.4, 1.2 Hz), 2.71 (1H, d, *J* = 14.4 Hz), 2.46-2.36 (2H, m), 2.23-2.15 (1H, m), 1.84-1.70 (5H, m), 1.27 (3H, s); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 213.9, 148.0, 128.7, 126.1, 125.7, 55.8, 44.3, 43.6, 39.9, 32.0, 25.9, 24.0. **Anal Calcd for $C_{14}H_{18}O$:** C, 83.12; H, 8.97; Found C, 82.92; H, 9.11; **HRMS (EI^+):** Calcd for $C_{14}H_{18}O$: 202.1358, Found: 202.1359; **Optical rotation:** $[\alpha]_D^{20}$ +74.78 (*c* = 1.00, $CHCl_3$) for a 96% ee sample.

Optical purity was determined by chiral GLC analysis in comparison with authentic

racemic material (96% ee sample below; conditions: α-dex column, 140 °C, 15 psi).



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	269.710	MM	1.9492	60.38792	5.16355e-1	50.06447
2	274.604	MM	2.0158	60.23238	4.97991e-1	49.93553



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	269.420	MM	1.5077	30.58191	3.38070e-1	2.13585
2	272.520	MM	2.3867	1401.25720	9.78508	97.86415

ν Representative experimental procedure for *direct* synthesis of enolsilanes

((*S*)-3-Methyl-3-phenylcyclohex-1-enyloxy)trimethylsilane (2.124). An oven-dried 13x100 mm test tube charged with **Ag-II** (5.6 mg, 0.0045 mmol), $(CuOTf)_2 \cdot C_6H_6$ (2.7 mg, 0.0045 mmol), 3-methyl-2-cyclohexenone (20 mg, 0.18 mmol), and Ph_2Zn (120 mg, 0.546 mmol), which were weighed out under N_2 atmosphere in a glove box. The reaction vessel was sealed with a septum and wrapped with parafilm before being removed from the glove box. Diethyl ether (1.0 mL) was slowly added at –78 °C. After 48 h at –30 °C, the reaction was cooled to –78 °C and TMSOTf (99 μL, 0.55 mmol) was added, followed by 2.0 mL of H_2O. The mixture was washed with Et_2O (3x1 mL). The volatiles were removed in vacuo and the resulting dark brown oil was purified by silica gel column chromatography (hexanes/Et_2O: 20/1) to afford 46.8 mg (0.180 mmol, >98% yield) of **2.124** as a colorless oil. (**Note:** Before the mixture was added, the silica gel column was eluted with 0.5 mL of Et_3N.) **IR (neat):** 3081 (w), 3057 (w), 3029 (w), 3020 (w), 2959 (s), 2934 (s), 2867 (w), 2853 (w), 2836 (w), 1665 (s), 1251 (s), 1195 (s), 895 (s), 865 (s),

847 (s), 760 (s), 697 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.43-7.31 (4H, m), 7.22-7.18 (1H, m), 4.99-4.98 (1H, m), 2.09-2.05 (2H, m), 1.87-1.82 (1H, m), 1.68-1.60 (2H, m), 1.52-1.44 (1H, m), 1.43 (3H, s), 0.28 (9H, s); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 150.7, 141.4, 128.0, 126.8, 125.7, 113.5, 40.1, 39.0, 30.3, 30.0, 19.7, 0.6; **HRMS (EI^+):** Calcd for $C_{16}H_{24}OSi$: 260.1596, Found: 260.1600.

ν Representative experimental procedure for synthesis of enolsilanes through deprotonation/trap of ACA products

((*S*)-5-Methyl-5-phenylcyclohex-1-enyloxy)trimethylsilane (2.125). A solution of *n*-BuLi (345 μL, 0.517 mmol, 1.5 M in hexanes) was added to a cold (–78 °C) THF (2 mL) solution of 2,2,6,6-tetramethyl piperidine (99 μL, 0.59 mmol). The mixture was allowed to warm to 22 °C, stirred for 5 min, and cooled again to –78 °C. Optically enriched ketone ent-**2.7** (65 mg, 0.34 mmol), dissolved in THF (1 mL), was added to the mixture, which was allowed to stir for 30 min at –78 °C. Trimethylsilyltriflate (187 μL, 1.03 mmol) was added and the mixture was allowed to stir for an additional 15 min at –78 °C. A saturated solution of $NaHCO_3$ (1.0 mL) was added and the mixture was allowed to warm slowly to 22 °C, at which time the solution was diluted through addition of H_2O (1 ml). The mixture was washed with Et_2O (3x1.0 mL) and the combined organic layers were concentrated in vacuo and the resulting light yellow oil purified by silica gel column chromatography (hexanes/Et_2O: 20/1) to afford 86 mg (0.33 mmol, 96% yield) of enolsilane **2.125** as a colorless oil. (**Note:** Before the mixture was added, the silica gel

column was eluted with 0.5 mL of Et_3N.) **IR (neat):** 3087 (w), 3056 (w), 3030 (w), 3024 (w), 2962 (s), 2924 (s), 2848 (m), 1671 (s), 1496 (m), 1443 (m), 1357 (m), 1251 (s), 1211 (s), 1186 (s), 1172 (s), 912 (s), 884 (s), 847 (s), 761 (s), 698 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.43-7.30 (4H, m), 7.24-7.19 (1H, m), 4.88-4.86 (1H, m), 2.51 (1H, d, *J* = 16.4 Hz), 2.15 (1H, d, *J* = 16.8 Hz), 2.11-2.05 (1H, m), 1.93-1.81 (2H, m), 1.75-1.68 (1H, m), 1.32 (3H, s), 0.25 (9H, s); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 149.4, 127.3, 128.1, 125.9, 125.8, 103.3, 42.4, 37.9, 34.7, 28.3, 21.7, 0.7; **HRMS (EI^+):** Calcd for $C_{16}H_{24}OSi$: 260.1596, Found: 260.1594.

■ **Representative procedure for *direct* synthesis of enoltriflate 2.126:** An oven-dried 13x100 mm test tube charged with **Ag-II (**3.1 mg, 0.0050 mmol), $(CuOTf)_2 \bullet C_6H_6$ (1.3 mg, 0.0025 mmol), and 3-methyl-2-cyclohexenone (10.0 mg, 0.100 mmol). All the above were weighed out under an N_2 atmosphere in a glove box. The test tube was sealed with a septum and wrapped with parafilm before the tube was removed from the glove box. Diethyl ether (750 μL) was added at 22 °C; the resulting solution was allowed to stir for 10 min. Diethylzinc (30 μL, 0.30 mmol) was added dropwise to the mixture after it was cooled to –78 °C; during the addition of Et_2Zn the mixture turned dark brown. After addition of diethylzinc, the mixture was allowed to warm to –30 °C. After 6 h at –30 °C, Tf_2O (168 mL, 1.0 mmol) was added to the mixture by a syringe. The mixture was immediately allowed to warm to 22 °C and stir for 1 h. The reaction was quenched by the addition of a saturated solution of aqueous sodium bicarbonate (1 mL) and H_2O (1 mL). The mixture was washed with petroleum ether (3 x 1 mL), and the combined

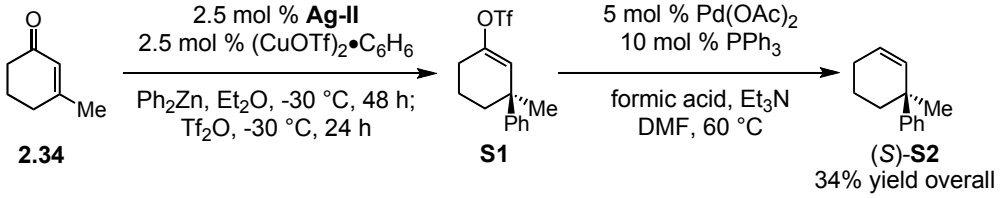
organic layers were passed through a short plug (4 cm x 1 cm) of silica gel eluted with petroleum ether to afford 27.0 mg (0.0992 mmol, 99.2% yield) of **2.126** as a colorless oil. **Important note:** To ensure high efficiency and enantioselectivity, reactions must be set up in exactly the order described above. The optical purity of the sample was obtained by treatment of the enoltriflate

(*R*)-3-Ethyl-3-methylcyclohex-1-enyl trifluoromethanesulfonate (2.126). IR (neat): 2966 (m), 2933 (m), 2856 (w), 1416 (s), 1257 (m), 1213 (s), 1153 (s), 1026 (w), 960 (w), 894 (w), 845 (w), 801 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.49 (1H, s), 2.32-2.19 (2H, m), 1.84-1.70 (2H, m), 1.50-1.30 (4H, m), 1.00 (3H, s), 0.83 (3H, t, J = 7.2 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 148.7, 127.2, 118.7 (q, J = 318.8 Hz), 36.2, 34.8, 33.8, 27.8, 26.4, 19.7, 8.4.

(*R*)-(3-Ethyl-3-methylcyclohex-1-enyl)benzene (2.127). An oven-dried vial was charged with $Pd(OAc)_2$ (1.0 mg, 0.0044 mmol), PPh_3 (2.5 mg, 0.0097 mmol), and $PhB(OH)_2$ (6.7 mg, 0.055 mmol) was weighed out under an N_2 atmosphere in a glovebox. The vial was sealed with a septum prior to removal from the glovebox. In a separate vial, enol triflate **21** (12.2 mg, 0.0448 mmol) dissolved in anhydrous THF (1.0 mL) was added to the vial containing $Pd(OAc)_2$, PPh_3, and $PhB(OH)_2$ through a syringe. The mixture was stirred for 10 min at 22 oC after which time aqueous KOH (0.5 M, 88 μL, 0.044 mmol) was added via syringe. After 45 min at 22 C the reaction was quenched with H_2O (1 mL) and extracted with EtOAc (4 x 1 mL). The combined organic extracts were dried

with MgSO4, filtered and concentrated to yield a dark brown oil, which was purified by silica gel column chromatography to afford 6.8 mg (0.033, 77%) of **2.127** as a colorless oil**. IR (neat):** 3029 (w), 2963 (s), 2936 (s), 2864 (m), 1607 (w), 1496 (w), 1447 (m), 1375 (m), 1006 (w), 879 (w), 768 (s), 697 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40-7.37 (2H, m), 7.32-7.27 (2H, m), 7.21 (1H, tt, *J* = 7.2, 1.6 Hz), 5.81 (1H, s), 2.41-2.82 (2H, m), 1.83-1.70 (2H, m), 1.57-1.50 (1H, m), 1.44-1.35 (3H, m), 1.01 (3H, s), 0.87 (3H, t, *J* = 7.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 142.9, 135.2, 134.5, 128.3, 126.7, 125.3, 35.4, 35.2, 33.9, 27.8, 27.0, 20.0, 8.6. **Optical Rotation:** $[\alpha]_D^{22}$ –20.4 (*c* 0.453, $CHCl_3$) for a sample of 87% ee.

■ **Proof of Absolute Stereochemistry.** The following sequence was carried out to obtain enantiomerically enriched material **S2**.



An oven-dried 13 x 100 mm test tube was charged with **Ag-II** (4.9 mg, 0.0081 mmol), $(CuOTf)_2•C_6H_6$ (2.0 mg, 0.0045 mmol), 3-ethyl-2-cyclohexenone (19.9 mg, 0.161 mmol) and diphenylzinc (106 mg, 0.483 mmol), which weighed out under a N_2 atmosphere in a glove box in the order presented. The test tube was sealed with a septum, wrapped with parafilm, and the reaction vessel was removed from the glove box. Diethyl ether (1.0 mL) was added to the mixture in a dropwise manner (syringe) at –78 °C. After 48 h at –30 °C, Tf_2O (142 μL, 0.850 mmol) was added at -30 °C through the septum via syringe

and the reaction mixture was kept at –30 °C for 24 h. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (1.0 mL) followed by addition of H_2O (1.0 mL). The mixture was then extracted with diethyl ether (3x1.0 mL) and passed through a short plug of silica gel eluted with diethyl ether. The volatiles were removed in vacuo and the resulting colorless oil was purified by silica gel column chromatography (100% hexanes) to afford 25.5 mg (0.081 mmol, 48.1% yield) of enoltriflate **2.126** as a colorless oil. **Important note:** To ensure high efficiency and enantioselectivity the reaction must be set up in exactly the order described above.

(*S*)-3-methyl-3-phenylcyclohex-1-enyl trifluoromethanesulfonate (S1): IR (neat): 2973 (w), 2938 (w), 1688 (w), 1422 (s), 1252 (m), 1222 (s), 1146 (s), 1016 (w), 906 (m), 876 (w), 845 (w), 765 (w), 710 (w), 620 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.34-7.29 (2H, m), 7.25-7.18 (3H, m), 5.96 (1H, s), 2.42-2.25 (2H, m), 1.95-1.85 (2H, m), 1.80-1.65 (3H, m), 1.54-1.43 (1H, m), 0.75 (3H, t, *J* = 7.2 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 150.3, 146.1, 128.6, 127.0, 126.4, 124.3, 118.8 (q, *J* = 318.1 Hz), 45.0, 35.9, 34.7, 28.0, 19.3, 8.7; **HRMS (EI^+):** Calcd for $C_{15}H_{17}O_3F_3S$: 334.0851, Found: 334.0848.

1-((*S*)-1-methylcyclohex-2-enyl)benzene (S2). An oven-dried vial was charged with $Pd(OAc)_2$ (0.98 mg, 0.0044 mmol) and PPh_3 (2.3 mg, 0.0088 mmol), which were weighed out under N_2 atmosphere in a glovebox. The vial was sealed with a septum, and removed from the glovebox. In a separate flask, enol triflate **22** (21 mg, 0.089 mmol) was dissolved in anhydrous DMF (1.0 mL) was added through a syringe. The mixture

was then charged with triethylamine (37.0 μL, 0.267 mmol), followed by formic acid (6.8 μL, 0.18 mmol), and was heated to 60 °C for 30 min, during which time the solution turned black. The mixture was cooled to 22 °C and diluted by the addition of H_2O (1.0 mL), followed by wash with petroleum ether (5x1.0 ml). The combined organic layers were passed through a short plug of silica gel eluting with petroleum ether. The filtrate was concentrated under reduced pressure to yield **23** as colorless oil (11.5 mg, 0.0167 mmol, 69.5% yield). **IR (neat):** 3065 (w), 3029 (w), 2981 (m), 2934 (s), 2874 (m), 2832 (w), 1499 (m), 1451 (m), 1374 (w), 1047 (w), 939 (w), 916 (w), 773 (s), 737 (m), 713 (s), 582 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.32-7.25 (4H, m), 7.17-7.12 (1H, m), 5.91-5.82 (2H, m), 2.01-1.97 (2H, m), 1.90-1.64 (4H, m), 1.58-1.50 (1H, m), 1.38-1.27 (1H, m), 0.73 (3H, t, *J* = 7.2 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 148.4, 133.0, 128.0, 127.9, 127.3, 125.5, 43.1, 36.8, 35.1, 25.7, 19.1, 8.8; **HRMS (EI^+):** Calcd for $C_{14}H_{18}$ 186.1409, Found: 186.1404; **Optical Rotation:** $[\alpha]_D^{20}$ –27.2 (*c* 0.780, $CHCl_3$) for an 40% ee sample. **Proof of stereochemistry.** The optical rotation of cyclic alkene **S2** was compared to a value reported previously by Breit et al, who assigned (+) rotation to the *R* enantiomer but did not provide an exact value.[120]

ν Preparation of *di*-4-methoxyphenyl zinc (2.105). Mg turnings (1.8 g, 75 mmol) were weighed out into a two-neck 50 mL round bottomed flask equipped with a reflux condenser. The apparatus was then flame-dried and allowed to cool under N_2.

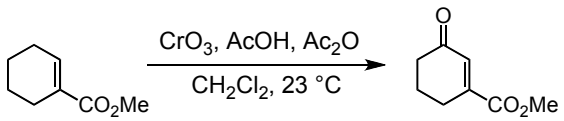
(120) "Stereospecific and Stereodivergent Construction of Quaternary Carbon Centers through Switchable Directed/Nondirected Allylic Substitution," Breit, B.; Demel, P.; Studte, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3786–3789.

Tetrahydrofuran (16 mL) was added, followed by the dropwise addition of 4-bromoanisole (6.2 mL, 50 mmol), such that gentle reflux could be maintained. The mixture was allowed to stir for 12 h. Titration indicated a 2.27 M solution of the Grignard reagent. (Note: Grignard reagent solution and syringe/needle must be kept warm during titration and addition because of the low solubility of the arylmetal in THF.)

An oven- and flame-dried 100 mL round bottomed flask (equipped with a stir bar) was charged with $ZnCl_2$ (1.4 g, 10 mmol) weighed out under an N_2 atmosphere; the flask was sealed with a septum and removed from the glovebox. Diethyl ether (20 mL) was added and the solution was allowed to cool to 0 °C. A solution of the above-mentioned Grignard reagent (8.8 mL, 20 mmol) was added dropwise through a syringe (within approximately 10 min). During addition, a significant amount of white precipitate is generated. The mixture was allowed to warm to 22 °C and stir for 2 h. At this time, the solution was charged with dioxane (10 mL) and allowed to stir for an additional 30 min. (Note: 10 mL of THF can be added at this point if the solution containing Zn reagent appears too viscous for proper filtration.) At this point, an oven-dried Schlenk tube (medium porosity filter) containing approximately 5 g of oven-dried celite and a 100 mL round bottomed flask on the receiving end was quickly exchanged with the septum on the flask containing the Zn reagent. This was performed such that the round-bottomed flask containing the Zn reagent remained in a horizontal position; this ensured that celite does not fall into the flask that contains the zinc reagent Filtration was then performed under an atmosphere of N_2. The filtrate was then concentrated in vacuo (~0.4 mm Hg), followed by gentle heating (still under vacuum; to assist in removal of dioxane) to afford

a white solid. The white solid was transferred to a sublimation apparatus under an atmosphere of N_2, and the white solid was sublimed under stronger vacuum (0.01 mmHg) at 150 °C to afford a white powder. **Note:** The ^{1}H NMR of this material is identical to the ^{1}H NMR of the diarylzinc reagent prior to sublimation. We find that Cu-catalyzed ACA with sublimed arylmetal samples deliver slightly higher levels of enantioselectivity. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.57 (4H, d, *J* = 8.4 Hz), 6.94 (4H, d, *J* = 8.8 Hz), 3.83 (6H, s); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 160.1, 139.2, 138.5, 114.0, 55.1.

■ **Representative experimental procedures for the preparation of methyl ester substrates 4-5b:**[121]

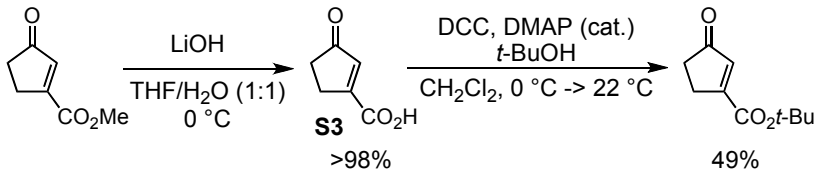


2.128

(121) (a) A similar procedure for the preparation of methyl-3-oxocyclohex-1-enecarboxylate and methyl-3-oxocyclopent-1-enecarboxylate has been reported, see: "Ring Expansions of [2 + 2] Photoadducts. Potential Applications in the Synthesis of Triquinane and Taxane Skeletons," G. L. Lang, C. D. Decicco, J. Willson, L. A. Strickland, *J. Org. Chem.* **1989**, *54*, 1805-1810. Though other catalytic allylic oxidation methods have been reported (see (b) and (c)) to afford **4-5b**, we found that product of the highest purity could be obtained with Cr-mediated allylic oxidation. (b) For Pd-catalyzed allylic oxidation, see: "A Mild, Catalytic, and Highly Selective Method for the Oxidation of α,β,-Enones to 1,4-Enediones," J-Q. Yu, E. J. Corey, *J. Am. Chem. Soc.* **2003**, *125*, 3232-3233. (c) For Rh-catalyzed allylic oxidation, see: "Dirhodium(II) Caprolactamate: An Exceptional Catalyst for Allylic Oxidation," A. J. Catino, R. E. Forslund, M. P. Doyle, *J. Am. Chem. Soc.* **2004**, *126*, 13622-13623.

Methyl-3-oxocyclohex-1-enecarboxylate (2.128). To a 100 mL round bottom flask charged with CrO_3 (9.22 g, 60.7 mmol) was added AcOH (28.6 mL, 500 mmol) and Ac_2O (14.5 mL, 142 mmol). The dark red mixture was allowed to stir for 1 h. In a 250 mL round bottom flask equipped with an addition funnel was added methyl-1-cyclohexene-1-carboxylate (5.00 g, 35.7 mmol) and CH_2Cl_2 (71 mL). The solution of CrO_3 in AcOH/Ac_2O was transferred to the addition funnel and slowly added to the CH_2Cl_2 solution of methyl-1-cyclohexene-1-carboxylate over 1 h. (During the addition of CrO_3 to the substrate, the solution becomes black.) The mixture was allowed to stir for an additional 1 h, at which time the solution was allowed to cool to 0 °C and the reaction quenched upon addition of a 10 M aq solution of KOH (~80 mL) until pH ~ 8. The mixture was then diluted with Et_2O (200 mL) and H_2O (200 mL). The organic layer was separated and the aqueous layer was washed with Et_2O (3 x 200 mL). The combined organic layers were then washed with a saturated aqueous solution of $NaHCO_3$ (3 x 200 mL) and brine (1 x 200 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to afford a yellow oil which was purified by silica gel column chromatography (5% Et_2O/petroleum ether -> 20% Et_2O/petroleum ether) then distilled under reduced pressure to yield 3.00 g (19.4 mmol, 54.3%) of **2.128** as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.72 (1H, t, *J* = 2.0 Hz, C**H**), 3.82 (3H, s, OC**H**$_3$) 2.57 (2H, td, *J* = 6.0, 2.0 Hz), 2.45-2.42 (2H, m), 2.07-2.01 (2H, m); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 200.2, 167.1, 149.0, 133.2, 52.7, 37.8, 25.0, 22.3.

■ **Representative experimental procedures for the preparation of *tert*-butyl ester substrates 4-5a:**



3-Oxocyclopent-1-enecarboxylic acid (S3). LiOH (1.50 g, 64.0 mmol) was added to methyl 3-oxocyclopent-1-enecarboxylate (1.80 g, 12.8 mmol) dissolved in THF (180 mL) and H_2O (180 mL) at 0 °C. The mixture was allowed to stir for two minutes, at which time the reaction was quenched upon addition of a 0.5 M solution of aqueous HCl (100 mL) at 0 °C until pH < 4. The mixture was washed with EtOAc (3 x 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to yield 1.50 g (12.8 mmol, >98.0% yield) of **S3** as a white solid, which was used directly in the subsequent reaction.

***tert*-Butyl-3-oxocyclopent-1-enecarboxylate.** To a solution of carboxylic acid **S3** (206 mg, 1.64 mmol), DMAP (39.0 mg, 0.320 mmol) and *t*-BuOH (235 μL, 2.46 mmol) dissolved in CH_2Cl_2 (15 mL) at 0 °C was added dropwise a solution of DCC (474 mg, 2.30 mmol) dissolved in CH_2Cl_2 (6.0 mL) through a syringe. The mixture was then allowed to warm to 22 ^oC (during which time the mixture becomes brown) and stir for 15 h. At this time, the mixture was diluted with Et_2O (20 mL) and passed through a short column of Celite 545 (2 x 5 cm) layered on top of silica gel (2 x 10 cm) eluted with Et_2O. The filtrate was concentrated in vacuo to afford a pale yellow oil, which was purified by

silica gel column chromatography (5% Et_2O/petroleum ether -> 20% Et_2O/petroleum ether) then distilled under reduced pressure to yield 146 mg (0.784 mmol, 49.0%) of *tert*-butyl 3-oxocyclopent-1-enecarboxylate as a clear oil. **IR (neat):** 2993 (m), 2945 (m), 1722 (s), 1721 (s), 1619 (m), 1443 (m), 1401 (m), 1377 (m), 1346 (m), 1249 (s), 1231 (s), 1153 (s), 1068 (m), 989 (w), 904 (w), 850 (w), 795 (w), 747 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.55 (1H, t, *J* = 2.0 Hz, C**H**), 2.72-2.69 (2H, m), 2.41-2.39 (2H, m), 1.43 (9H, s, C(C**H**$_3$)$_3$); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 209.3, 166.2, 163.4, 137.3, 82.4, 35.6, 27.9, 27.4; **HRMS (CI+):** Calcd for $C_{10}H_{15}O_3$: 183.102120 [M^++H], Found: 183.101802.

***tert*-Butyl-3-oxocyclohex-1-enecarboxylate. IR (neat):** 2984 (m), 2964 (m), 2875 (w), 1717 (s), 1690 (s), 1468 (w), 1387 (m), 1273 (s), 1165 (s), 1073 (m), 1029 (w), 975 (w), 905 (w), 851 (w), 742 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.65 (1H, t, *J* = 2.0 Hz, C**H**), 2.52 (2H, dt, *J* = 6.0, 2.0 Hz), 2.41, (2H, dd, *J* = 8.0, 6.8 Hz), 2.02 (2H, tt, *J* = 6.0, 6.0 Hz), 1.49 (9H, s, C(C**H**$_3$)$_3$); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 200.8, 165.8, 151.1, 132.5, 82.4, 37.9, 28.1, 25.0, 22.4; **HRMS (CI+):** Calcd for $C_{11}H_{17}O_3$ [M^++H]: 197.117770, Found: 197.117307.

■ **Representative experimental procedure for Cu-catalyzed conjugate addition of *Me_2Zn* to unsaturated cyclic *γ*-ketoesters:** An oven-dried 13x100 mm test tube was charged with **Ag-III** (3.02 mg, 2.50 μmol) and $(CuOTf)_2 \bullet C_6H_6$ (1.30 mg, 2.50 μmol),

weighed out under a N_2 atmosphere in a glove box. The test tube was sealed with a septum and wrapped with parafilm before removal from the glove box. *tert*-Butylmethylether (1.0 mL) was added through a syringe and the resulting solution was allowed to stir for five minutes before cooling to –78 °C (dry ice/acetone bath). Dimethylzinc (21.0 μL, 0.300 mmol) (PYROPHORIC, USE EXTREME CAUTION) was added and the resulting light yellow mixture was allowed to warm to –30 °C (cryocool). (During this time the mixture became dark brown.) After 10 minutes at –30 ^{o}C, methyl 3-oxocyclohex-1-enecarboxylate (13.4 μL, 15.4 mg, 0.100 mmol) was added to the mixture through a syringe.[122] After 15 h at –30 °C, the reaction was quenched upon addition of a saturated aqueous solution of ammonium chloride (1 mL) and H_2O (1 mL). After allowing the mixture to warm to 22 °C, it was washed with EtOAc (2 x 1 mL) and passed through a short plug of silica gel (4 cm x 1 cm) eluted with EtOAc. The volatiles were removed in vacuo, resulting in a yellow oil that was purified by silica gel column chromatography (5% Et_2O/petroleum ether -> 20% Et_2O/petroleum ether) to afford 15.1 mg of the desired product as a clear oil (0.0888 mmol, 88.8%).

■ **Representative experimental procedure for Cu-catalyzed conjugate addition of *Et_2Zn*, *$[(Me)_2CH(CH_2)_2]_2Zn$* and *$i\text{-}Pr_2Zn$*[123] to unsaturated cyclic γ-ketoesters:** An oven-dried 13x100 mm test tube was charged with chiral **Ag-III** (3.02 mg, 2.50 μmol) and $(CuOTf)_2 \bullet C_6H_6$ (1.30 mg, 2.50 μmol), weighed out under a N_2 atmosphere in a glove

(122) Methyl 3-oxocyclopent-1-enecarboxylate (white solid) was added as a solution in *t*-BuOMe (250 μL).
(123) *i*-Pr_2Zn was used as a 1.0 M solution in toluene (Aldrich).

box. The test tube was sealed with a septum and wrapped with parafilm before removal from the glove box. *tert*-Butylmethylether (1.0 mL) was added through a syringe and the resulting solution was allowed to stir for five minutes before cooling to –30 °C (dry ice/acetone bath). Diethylzinc (30.7 μL, 0.300 mmol) (PYROPHORIC, USE EXTREME CAUTION) followed by methyl 3-oxocyclopent-1-enecarboxylate (14.0 mg, 0.100 mmol) dissolved in *t*-BuOMe (250 μL) were added through a syringe.[124] (During the addition of Et_2Zn the mixture became dark brown.) After 1 h at –30 °C, the reaction was quenched upon addition of a saturated aqueous solution of ammonium chloride (1 mL) and H_2O (1 mL). After allowing the mixture to warm to 22 °C, it was washed with EtOAc (2 x 1 mL) and passed through a short plug of silica gel (4 cm x 1 cm) eluted with EtOAc. The volatiles were removed in vacuo, resulting in a yellow oil that was purified by silica gel column chromatography (5% Et_2O/petroleum ether -> 20% Et_2O/ petroleum ether) to afford 14.9 mg of the desired product as a clear oil (0.0876 mmol, 87.6%).

■ **Representative experimental procedure for Cu-catalyzed conjugate addition of *Me_2Zn* to unsaturated cyclic *γ*-ketoesters *set up on a bench top and carried out in undistilled t-BuOMe*:** A 13x100 mm test tube was charged with chiral **Ag-III** (3.02 mg, 2.50 μmol) and $(CuOTf)_2$•toluene (1.30 mg, 2.50 μmol), weighed out on a bench top. The test tube was sealed with a septum and wrapped with parafilm before being purged with N_2 for five minutes. Undistilled *t*-BuOMe (1.0 mL) was added through a syringe

(124) Substrates were added neat through a syringe with the exception of methyl 3-oxocyclopent-1-enecarboxylate.

and the resulting solution was allowed to stir for five minutes before cooling to –78 °C (dry ice/acetone bath). Dimethylzinc (21.0 μL, 0.300 mmol) (PYROPHORIC, USE EXTREME CAUTION) was added and the resulting light yellow mixture was allowed to warm to –30 ^{o}C (cryocool). (During this time the mixture became dark brown.) After 10 minutes at –30 ^{o}C, methyl 3-oxocyclohex-1-enecarboxylate (13.4 μL, 15.4 mg, 0.100 mmol) was added to the mixture through a syringe.[122] After 15 h at –30 °C, the reaction was quenched upon addition of a saturated aqueous solution of ammonium chloride (1 mL) and H_2O (1 mL). After allowing the mixture to warm to 22 °C, it was washed with EtOAc (2 x 1 mL) and passed through a short plug of silica gel (4 cm x 1 cm) eluted with EtOAc. The volatiles were removed in vacuo, resulting in a yellow oil that was purified by silica gel column chromatography (5% Et_2O/petroleum ether -> 20% Et_2O/petroleum ether) to afford 12.3 mg of the desired product as a clear oil (0.0723 mmol, 72.3%).

■ **Representative experimental procedure for Cu-catalyzed conjugate addition of *Ph_2Zn* to unsaturated cyclic *γ*-ketoesters:** An oven-dried 13x100 mm test tube was charged with **Ag-III** (3.02 mg, 2.50 μmol), $(CuOTf)_2 \bullet C_6H_6$ (1.3 mg, 2.50 μmol), and Ph_2Zn (65.7 mg, 0.300 mmol), weighed out under a N_2 atmosphere in a glove box. The test tube was sealed with a septum and wrapped with parafilm prior to removal from the glove box. The test tube containing the solids was allowed to cool to –30 °C (dry ice/acetone bath) and Et_2O (1.0 mL) was added through a syringe. The resulting mixture was allowed to stir for 10 minutes. (During this time the mixture became dark brown.) At this time, a solution of methyl 3-oxocyclopent-1-enecarboxylate (15.4 mg, 0.100

mmol) in Et_2O (500 μL) was added to the mixture through a syringe.[124] After 42 h at –30 °C, the reaction was quenched upon addition of a saturated aqueous solution of ammonium chloride (1 mL) and H_2O (1 mL). After allowing the mixture to warm to 22 °C, it was washed with EtOAc (2 x 1 mL) and passed through a short plug of silica gel (4 cm x 1 cm) eluted with EtOAc. The volatiles were removed in vacuo, to afford a yellow oil that was purified by silica gel chromatography (10% Et_2O/petroleum ether) to yield 15.3 mg (0.0701 mmol, 70.1%) of the desired product as a clear oil.

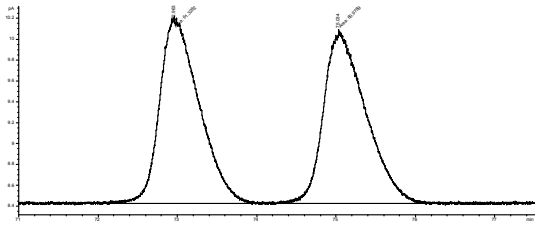
■ **Representative experimental procedure for Cu-catalyzed conjugate addition of *in-situ prepared* Ph_2Zn to unsaturated cyclic γ-ketoesters:** An oven-dried 13x100 mm test tube was charged with chiral **Ag-II** (3.07 mg, 2.50 μmol) and $(CuOTf)_2 \bullet C_6H_6$ (1.3 mg, 2.50 μmol), weighed out under a N_2 atmosphere in a glove box. The test tube was sealed with a septum and wrapped with parafilm prior to removal from the glove box. The test tube containing the solids was allowed to cool to –30 °C (dry ice/acetone bath). Another oven-dried 13x100 mm test tube was charged with $ZnCl_2$ (0.124 g, 0.900 mmol), weighed out under a N_2 atmosphere in a glove box. The test tube was sealed with a septum and wrapped with parafilm prior to removal from the glove box. Diethyl ether (2.2 mL) was added through a syringe to the test tube containing $ZnCl_2$, first allowing the $ZnCl_2$ to dissolve and then allowing the mixture to cool to 0 °C. Phenyllithium (818 μL, 1.80 mmol, 2.20 M in *n*-Bu_2O) was added dropwise through a syringe to the test tube containing a solution of $ZnCl_2$ in Et_2O and allowed to stir at 22 °C for 15 minutes. During this time the solution of PhLi + $ZnCl_2$ became cloudy. The test tube, now

containing a solution of Ph_2Zn and solid LiCl, was centrifuged for 15 minutes to assist with settling of the LiCl to the bottom of the test tube. At this time, 1.0 mL of the Ph_2Zn solution was added through a syringe to the test tube containing $(CuOTf)_2 \bullet C_6H_6$ and chiral Ag complex **2**, cooled to –30 °C (dry ice/acetone). The resulting mixture was allowed to stir for five minutes. A solution of methyl 3-oxocyclohex-1-enecarboxylate (15.4 mg, 0.100 mmol) in Et_2O (500 μL) was added through a syringe. After 24 h at –30 °C (cryocool), the reaction was quenched upon addition of a saturated aqueous solution of ammonium chloride (1 mL) and H_2O (1 mL). After allowing the mixture to warm to 22 °C, it was washed with EtOAc (2 x 1 mL) and passed through a short plug of silica gel (4 cm x 1 cm) eluted with EtOAc. The volatiles were removed in vacuo, to afford a yellow oil that was purified by silica gel chromatography (10% Et_2O/petroleum ether) to yield 19.0 mg (0.0820 mmol, 82.0%) of the desired product as a white solid.

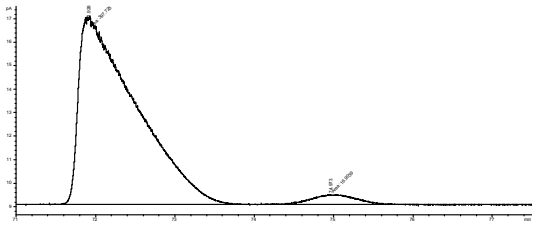
(*R*)-Methyl-1-methyl-3-oxocyclopentanecarboxylate (ent-2.65). IR (neat): 2963 (m), 2929 (m), 2886 (w), 2750 (s), 1721 (s), 1475 (m), 1442 (m), 1413 (m), 1336 (m), 1244 (m), 1220 (s), 1177 (m), 1110 (m), 994 (w), 879 (w), 787 (w) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 3.70 (3H, s, OC**H**$_3$), 2.74 (1H, d, *J* = 18.4 Hz, C(O)C**H**HC), 2.41-2.27 (3H, m, C(O)CH_2CH_2C), 2.10 (1H, d, *J* = 18.4 Hz, C(O)CH**H**C), 1.94-1.87 (1H, m, C(O)CH_2CH_2C), 1.36 (3H, s, CC**H**$_3$); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 217.1, 177.0, 52.6, 49.4, 46.5, 36.9, 34.0, 24.1; **HRMS (EI+):** Calcd for $C_8H_{11}O_3$ [M^+-H]: 155.070819,

Found: 155.071395; **Optical Rotation:** $[\alpha]_D^{20}$ –12.7 (*c* 1.50, $CHCl_3$) for an enantiomerically enriched sample of 92% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (92% ee shown; β-dex column, 15 psi, 90 °C).



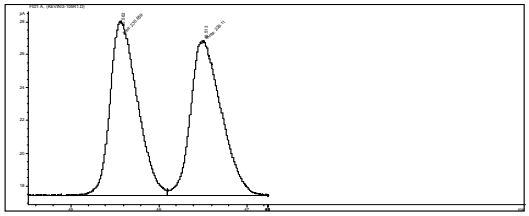
#	Time	Area	Height	Width	Area (%)
1	72.963	61.3	1.8	0.567	50.142
2	75.034	61	1.7	0.6099	49.858



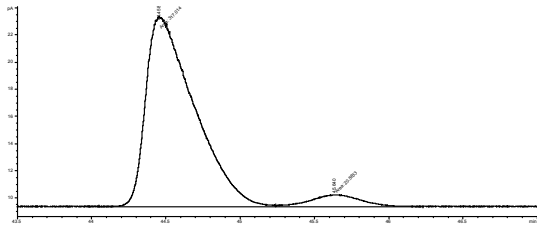
#	Time	Area	Height	Width	Area%
1	71.928	397.7	8	0.8242	95.923
2	74.973	16.9	4.2E-1	0.6733	4.077

(*R*)-Methyl-1-ethyl-3-oxocyclopentanecarboxylate (ent-2.57). IR (neat): 2977 (m), 2885 (w), 1759 (s), 1729 (s), 1466 (w), 1350 (w), 1258 (m), 1203 (m), 1166 (m), 995 (w) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 3.68 (3H, s, OC**H**$_3$), 2.73 (1H, d, *J* = 18.4 Hz, C(O)C**H**HC), 2.36 (1H, ddd, *J* = 8.4, 7.2, 1.2 Hz, $CH_2CH_2C(O)$), 2.25 (2H, dd, *J* = 7.2, 7.2 Hz, $CH_2CH_2C(O)$), 2.09 (1H, d, *J* = 18.4 Hz, C(O)CH**H**C), 1.92-1.79 (2H, m, $CH_2CH_2C(O)$ and C**H**HCH$_3$), 1.68-1.59 (1H, m, CH**H**CH$_3$), 0.85 (3H, t, *J* = 7.6 Hz, C**H**$_3$); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 217.1, 176.3, 52.4, 51.8, 47.1, 36.9, 32.4, 31.3, 10.1; **HRMS (EI+):** Calcd for $C_9H_{14}O_3$: 170.0943, Found: 170.0941; **Optical Rotation:** $[\alpha]_D^{20}$ –45.1 (*c* 0.286, $CHCl_3$) for an enantiomerically enriched sample of 88% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (88% ee shown; β-dex column, 15 psi, 110 °C).



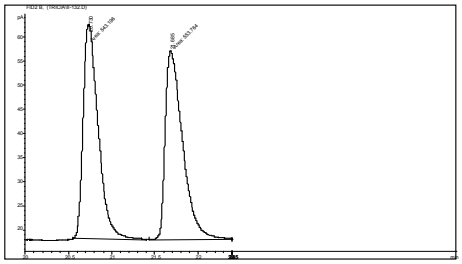
#	Time	Area	Height	Width	Area%
1	45.562	230.7	10.6	0.3611	50.168
2	46.513	229.1	9.4	0.4054	49.832



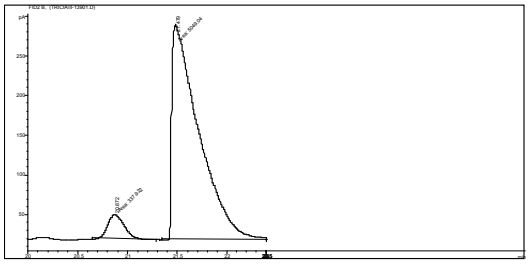
#	Time	Area	Height	Width	Area%
1	44.458	317	14	0.377	93.909
2	45.64	20.6	8.8E-1	0.3916	6.091

(*R*)-Methyl-1-(4-methylpentyl)-3-oxocyclopentanecarboxylate (2.114). IR (neat): 2955 (m), 2867 (w), 1747 (s), 1734 (s), 1457 (w), 1407 (w), 1388 (w), 1369 (w), 1338 (w), 1205 (m), 1155 (s), 985 (w), 872 (w) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 3.72 (3H, s, OC**H**$_3$), 2.79 (1H, dd, *J* = 18.4, 1.2 Hz, C(O)C**H**HC), 2.43-2.36 (1H, m), 2.28 (2H, t, *J* = 8.8 Hz, ($CH_2CH_2C(O)$), 2.12 (1H, d, *J* = 18.4 Hz, C(O)CH**H**C), 1.95-1.87 (1H, m), 1.83-1.76 (1H, m), 1.60-1.48 (2H, m), 1.26-1.12 (4H, m), 0.86 (3H, s, $CHCH_3C$**H**$_3$), 0.84 (3H, s, CHC**H**$_3CH_3$); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 217.1, 176.5, 52.4, 51.3, 47.6, 39.2, 38.8, 36.9, 32.9, 27.9, 23.6, 22.7, 22.7; **HRMS (EI^+):** Calcd for $C_{13}H_{22}O_3$: 226.1569, Found: 226.1569; **Optical Rotation:** $[\alpha]_D^{20}$ –30.8 (*c* 0.647, $CHCl_3$) for an enantiomerically enriched sample of 87% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (87% ee shown; chiral dex GTA column, 15 psi, 140 ^oC).



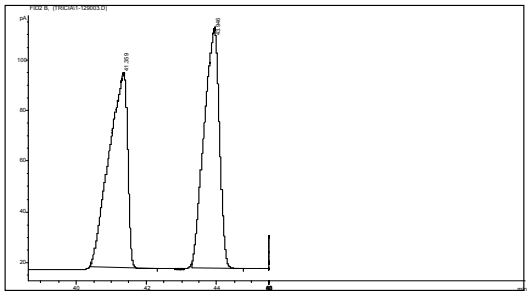
#	Time	Area	Height	Width	Area (%)
1	20.73	543.2	44.4	0.2039	49.518
2	21.685	553.8	39.3	0.2351	50.482



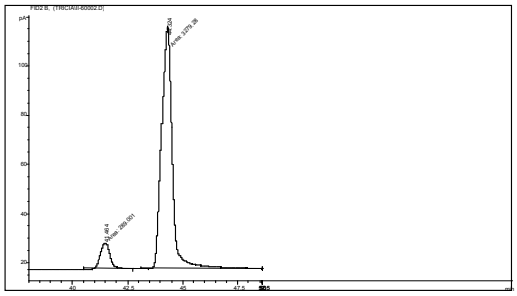
#	Time	Area	Height	Width	Area (%)
1	20.872	337.9	30.2	0.1864	6.273
2	21.479	5049	269.6	0.3122	93.727

(*R*)-Methyl-3-oxo-1-phenylcyclopentanecarboxylate (2.120). IR (neat): 2962 (w), 2924 (m), 2848 (w), 1753 (s), 1734 (s), 1445 (w), 1249 (m), 1212 (m), 1162 (m), 752 (m), 695 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.24 (5H, m, Ar**H**), 3.64 (3H, s, OC**H**$_3$), 3.23 (1H, dd, *J* = 16.0, 2.0 Hz, C(O)CH**H**C), 2.98-2.95 (1H, m, C(O)CH$_2$C**H**$_2$), 2.62 (1H, d, *J* = 18.0 Hz, C(O)C**H**HC), 2.35-2.32 (3H, m, C(O)C**H**$_2$CH$_2$C and C(O)CH$_2$CH**H**C); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 215.6, 175.0, 141.3, 129.0, 127.8, 126.6, 55.2, 53.1, 48.4, 37.2, 33.0; **Elemental Analysis:** Anal Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47; Found C, 71.53; H, 6.68.; **Optical Rotation:** $[\alpha]_D^{20}$ -7.05 (*c* 0.313, $CHCl_3$) for an enantiomerically enriched sample of 83% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (84% ee shown; chiral dex GTA column, 15 psi, 140 ^oC).



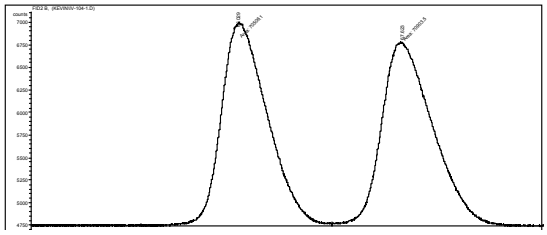
#	Time	Area	Height	Width	Area (%)
1	41.359	2848.3	77.1	0.4342	49.748
2	43.946	2877.2	94.9	0.3579	50.252



#	Time	Area	Height	Width	Area (%)
1	41.464	289	10.3	0.4693	8.099
2	44.324	3279.3	97.7	0.5593	91.901

(*R*)-*tert*-Butyl-1-methyl-3-oxocyclopentanecarboxylate (ent-2.66). IR (neat): 2983 (m), 2946 (w), 2879 (w), 1759 (s), 1729 (s), 1613 (w), 1466 (w), 1368 (m), 1246 (m), 1160 (s), 1111 (m), 854 (m) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 2.70 (1H, d, *J* = 18.0 Hz, C(O)C**H**HC), 2.41-2.24 (3H, m, $CH_2CH_2C(O)$), 2.06 (1H, d, *J* = 18.0 Hz, C(O)CH**H**C), 1.91-1.82 (1H, m, $CH_2CH_2C(O)$), 1.44 (9H, s, $C(CH_3)_3$), 1.33 (3H, s, CH_3); **^{13}C NMR ($CDCl_3$, 100 MHz):** 217.6, 175.7, 81.3, 49.5, 47.2, 37.1, 34.1, 28.1, 24.1; **HRMS (CI+):** Calcd for $C_{11}H_{19}O_3$ [M^++H]: 199.133420, Found: 199.133352; **Optical Rotation:** $[\alpha]_D^{20}$ –21.3 (*c* 1.05, $CHCl_3$) for an enantiomerically enriched sample of 90% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (89% ee shown; β-dex column, 15 psi, 100 °C).



#	Time	Area	Height	Width	Area (%)
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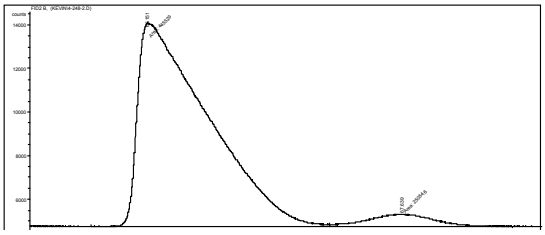
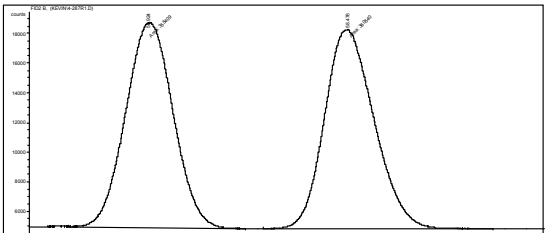


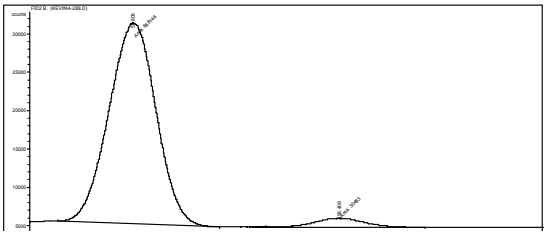
#	Time	Area	Height	Width	Area (%)
1	65.151	445508.2	9378.6	0.7917	94.675
2	67.639	25054.6	561.7	0.7434	5.325

(*R*)-*tert*-Butyl-1-isopropyl-3-oxocyclopentanecarboxylate (2.115). IR (neat): 2975 (m), 2929 (w), 2877 (w), 1752 (s), 1718 (s), 1463 (w), 1376 (m), 1266 (m), 1156 (s), 854 (w), 675 (w) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 2.75 (1H, d, *J* = 18.4 Hz, C(O)C**H**HC), 2.42-2.36 (1H, m, $CH_2CH_2C(O)$), 2.31-2.14 (2H, m, $CH_2CH_2C(O)$), 2.06-1.95 (2H, m, C(O)CH**H**C and C**H**$(CH_3)_2$), 1.86 (1H, ddd, *J* = 13.2, 10.4, 10.4 Hz, $CH_2CH_2C(O)$), 1.44 (9H, s, C(C**H**$_3)_3$), 0.95 (6H, dd, *J* = 8.0 Hz, CH(C**H**$_3)_2$); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 217.7, 174.7, 81.4, 56.2, 45.4, 37.5, 35.2, 30.8, 28.1, 18.7, 18.5; **HRMS (CI+):** Calcd for $C_{13}H_{23}O_3$: 227.164720 [M^++H], Found: 227.164414; **Optical Rotation:** $[\alpha]_D^{20}$ –100 (*c* 0.893, $CHCl_3$) for an enantiomerically enriched sample of 91% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (91% ee shown; β-dex column, 15 psi, 120 ^oC).



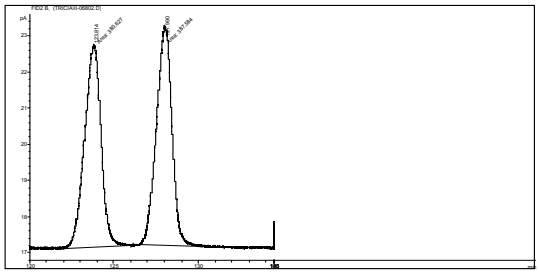
#	Time	Area	Height	Width	Area (%)
1	56.924	355409.4	13815.9	0.4287	49.599
2	58.476	360539.9	13413.4	0.448	50.400



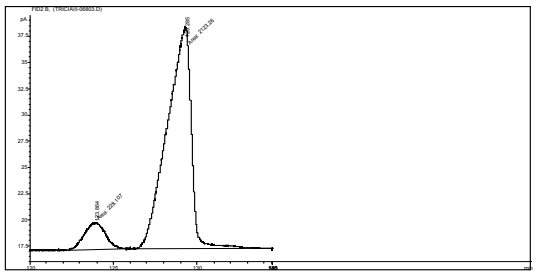
#	Time	Area	Height	Width	Area (%)
1	56.805	668145.7	26211	0.4248	95.618
2	58.409	30483	1143.6	0.4443	4.382

(*R*)-*tert*-Butyl-3-oxo-1-phenylcyclopentanecarboxylate (2.121). mp: 69-74 ^{o}C; **IR (neat):** 2950 (m), 2930 (m), 1747 (s), 1722 (s), 1596 (w), 1501 (w), 1451 (w), 1394 (w), 1369 (m), 1148 (s), 847 (m), 702 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.25 (5H, m, Ar**H**), 3.20 (1H, dd, *J* = 18.0, 2.0 Hz, C(O)C**H**HC), 2.96-2.90 (1H, m, C(O)CH_2CH**H**), 2.54 (1H, d, *J* = 18.0 Hz, C(O)CH**H**C), 2.35-2.25 (3H, m, C(O)C**H**$_2$$CH_2$ and C(O)CH_2CH**H**), 1.33 (9H, s, C(C**H**$_3$)$_3$); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 216.3, 173.5, 141.8, 128.8, 127.5, 126.6, 82.0, 55.9, 48.4, 37.3, 33.0, 27.9; **HRMS (CI+):** Calcd for $C_{16}H_{21}O_3$: 261.1492 [M^++H], Found 261.1491; **Optical Rotation:** $[\alpha]_D^{20}$ -7.11 (*c* 0.780, $CHCl_3$) for an enantiomerically enriched sample of 79% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (80% ee shown; chiral dex GTA column, 15 psi, 120 ^{o}C).



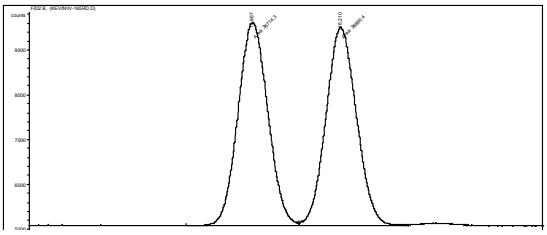
#	Time	Area	Height	Width	Area (%)
1	123.814	380.6	5.6	1.133	49.547
2	127.99	387.6	6.1	1.0667	50.453



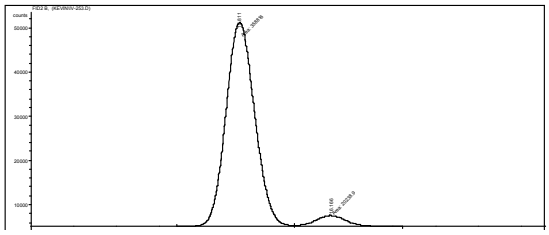
#	Time	Area	Height	Width	Area (%)
1	123.864	228.1	2.6	1.4718	9.701
2	129.285	2123.3	21.2	1.6727	90.299

(*R*)-Methyl-1-methyl-3-oxocyclohexanecarboxylate (2.111). IR (neat): 2952 (m), 2877 (w), 1734 (s), 1462 (m), 1318 (w), 1208 (m), 1168 (m), 1139 (m), 1110 (m); **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 3.61 (3H, s, OC**H**$_3$), 2.66 (1H, dt, *J* = 14.8, 1.6 Hz, CC**H**HC(O)), 2.31-2.24 (1H, m, $CCH_2CH_2CH_2C(O)$), 2.21-2.13 (1H, m, $CCH_2CH_2CH_2C(O)$, 2.11-2.02 (3H, m, $CCH_2CH_2CH_2C(O)$ and CCH**H**C(O)), 1.89-1.79 (1H, m, $CCH_2CH_2CH_2C(O)$), 1.73-1.60 (2H, m, $CCH_2CH_2CH_2C(O)$), 1.19 (3H, s, CC**H**$_3$); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 209.3, 176.6, 52.3, 50.0, 46.7, 40.3, 34.7, 24.8, 22.2; **HRMS (EI+):** Calcd for $C_9H_{14}O_3$: 170.094294, Found: 170.094668; **Optical Rotation:** $[\alpha]_D^{20}$ –17.7 (*c* 1.66, $CHCl_3$) for an enantiomerically enriched sample of 79% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (89% ee shown; β-dex column, 15 psi, 140 ^{o}C).



#	Time	Area	Height	Width	Area (%)
1	15.867	36714.3	4530.7	0.1351	50.035
2	16.21	36690.4	4424.2	0.1382	49.964



#	Time	Area	Height	Width	Area (%)
1	15.811	358815.7	46138.6	0.1296	94.734
2	16.166	20238.9	2447.1	0.1378	5.265

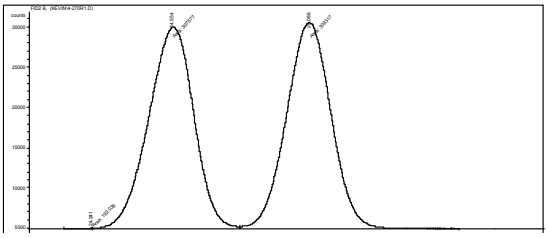
Proof of absolute stereochemistry: Basic hydrolysis (LiOH (5.0 equiv), THF/H_2O (0.8 M/0.8 M) 0 ºC -> 22 °C, 30 minutes, 68% yield, unoptimized) of (*R*)-methyl 1-methyl-3-oxocyclohexanecarboxylate (**2.111**) yielded (*R*)-1-methyl-3-oxocyclohexanecarboxylic acid. $[\alpha]_D^{20}$ –13.1 (*c* 0.806, $CHCl_3$) for an enantiomerically enriched sample of 79% ee. Literature: $[\alpha]_D^{22}$ –14.0 (*c* 1.00, $CHCl_3$) for an enantiomerically enriched sample of 85% ee in the *R* enantiomer.[125]

(*R*)-Methyl-1-ethyl-3-oxocyclohexanecarboxylate (2.116). IR (neat): 2953 (m), 2880 (w), 1734 (s), 1572 (w), 1543 (w), 1462 (m), 1373 (w), 1240 (m), 1203 (m), 1159 (m), 1139 (m), 1029 (m), 1001 (w); **^{1}H NMR ($CDCl_3$, 400 MHz):** 3.67 (3H, s, OC**H**$_3$), 2.77 (1H, dt, *J* = 14.8, 1.6 Hz, C(O)C**H**HC), 2.38-2.32 (1H, m, C(O)$CH_2CH_2CH_2$), 2.26-2.18 (1H, m, C(O)$CH_2CH_2CH_2$), 2.13-2.10 (2H, m, C(O)$CH_2CH_2CH_2$ and C(O)CH**H**C), 1.95-1.85 (1H, m, C(O)$CH_2CH_2CH_2$), 1.80-1.61 (3H, m, C(O)$CH_2CH_2CH_2$ and C**H**HCH_3), 1.53 (1H, dq, *J* = 15.2, 7.6 Hz, CH**H**CH_3) 0.81 (3H, t, *J* = 7.6 Hz, C**H**$_3$); **^{13}C NMR**

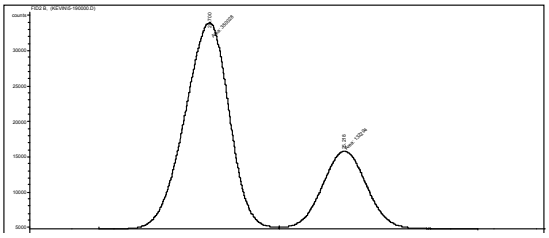
(125) "Formaldehyde Dialkylhydrazones as Neutral Formyl Anion and Cyanide Equivalents: Nucleophilic Addition to Conjugated Enones," Díez, E.; Fernández, R.; Gasch, C.; Lassaletta, J. M.; Llera, J. M.; Martín-Zamora, E.; Vázquez, J. *J. Org. Chem.* **1997**, *62*, 5144-5155.

($CDCl_3$, 100 MHz): 209.4, 176.0, 52.2, 51.2, 47.6, 40.7, 33.4, 31.8, 22.2, 8.8; **HRMS (EI+):** Calcd for $C_{10}H_{16}O_3$: 184.109945, Found: 184.109718; **Optical Rotation:** $[\alpha]_D^{20}$ – 11.3 (*c* 1.31, $CHCl_3$) for an enantiomerically enriched sample of 42% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (45% ee shown; β-dex column, 15 psi, 140 °C).



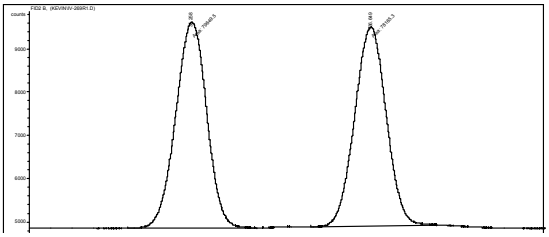
#	Time	Area	Height	Width	Area (%)
1	24.554	307577.2	25085.4	0.2044	49.885
2	25.086	309317.2	25659.1	0.2009	50.114



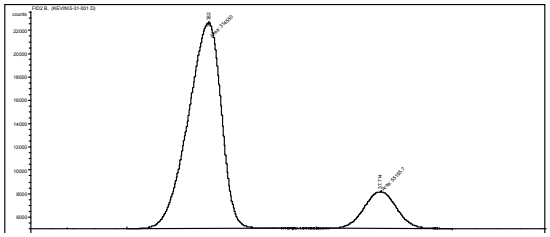
#	Time	Area	Height	Width	Area (%)
1	24.7	350028.2	29102.8	0.2005	72.554
2	25.218	132294.2	10986.3	0.2007	27.445

(*R*)-Methyl-1-isopropyl-3-oxocyclohexanecarboxylate (2.117). IR (neat): 2969 (m), 2877 (w), 1741 (s), 1567 (w), 1451 (m), 1382 (m), 1295 (m), 1242 (m), 1208 (m), 1167 (m), 1127 (m), 1092 (m), 988 (w), 889 (w), 750 (w) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 3.66 (3H, s, OC**H**$_3$), 2.70 (1H, dt, *J* = 14.8, 2.4 Hz, CC**H**HC(O)), 2.40-2.33 (1H, m, $CH_2CH_2CH_2C(O)$), 2.21-1.91 (5H, m, $CH_2CH_2CH_2C(O)$, C**H**$(CH_3)_2$ and CCH**H**C(O), 1.75 (1H, dt, *J* = 12.8, 3.6 Hz, $CH_2CH_2CH_2C(O)$), 1.58-1.46 (1H, m, $CH_2CH_2CH_2C(O)$), 0.91 (3H, d, *J* = 6.8 Hz, CHC**H**$_3$), 0.84 (3H, d, *J* = 6.8 Hz, CHC**H**$_3$); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 209.8, 176.1, 65.0, 54.7, 52.1, 43.8, 40.6, 34.9, 31.9, 22.4, 18.2, 17.2; **HRMS (EI+):** Calcd for $C_{11}H_{18}O_3$: 198.125595, Found: 198.126392; **Optical Rotation:** $[\alpha]_D^{20}$ –23.8 (*c* 0.673, $CHCl_3$) for an enantiomerically enriched sample of 70% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (70% ee shown; β-dex column, 15 psi, 140 °C).



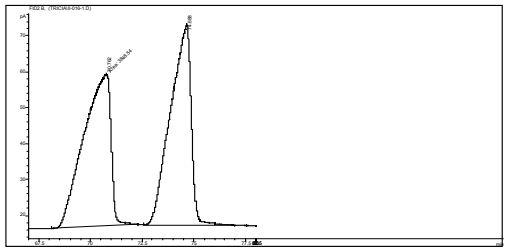
#	Time	Area	Height	Width	Area (%)
1	35.258	79649.5	4750.4	0.2794	50.546
2	36.649	78165.3	4595.4	0.2835	49.454



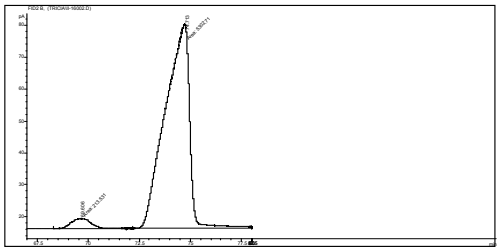
#	Time	Area	Height	Width	Area (%)
1	36.382	314549.9	17661.7	0.2968	84.851
2	37.714	55165.7	3147.9	0.2921	15.149

(*R*)-Methyl-3-oxo-1-phenylcyclohexanecarboxylate (2.122). mp: 96-98 °C; **IR (neat):** 2974 (m), 2961 (m), 2955 (m), 2879 (w), 1727 (s), 1495 (w), 1451 (m), 1325 (m), 1300 (m), 1249 (s), 1211 (s), 1155 (m), 1111 (m), 985 (w), 885 (w), 783 (w), 746 (m), 714 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36-7.28 (4H, m, Ar**H**), 7.28-7.24 (1H, m, Ar**H**), 3.64 (3H, s, OC**H**$_3$), 3.04 (1H, dt, *J* = 14.8, 1.6 Hz, C(O)C**H**HC), 2.74 (1H, d, *J* = 14.8 Hz, C(O)CH**H**), 2.57-2.51 (1H, m, CC**H**$_2$CH$_2$), 2.42-2.24 (3H, m, CC**H**$_2$CH$_2$ and C(O)C**H**H), 1.88-1.66 (2H, m, C(O)CH$_2$C**H**$_2$); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 208.8, 174.9, 141.3, 129.1, 127.7, 126.2, 54.1, 52.8, 49.5, 40.5, 33.3, 21.7; **HRMS (EI+):** Calcd for $C_{14}H_{16}O_3$: 232.2750, Found 232.1096; **Optical Rotation:** $[\alpha]_D^{20}$ –4.61 (*c* 0.700, $CHCl_3$) for an enantiomerically enriched sample of 92% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (92% ee shown; chiral dex GTA column, 15 psi, 140 °C).

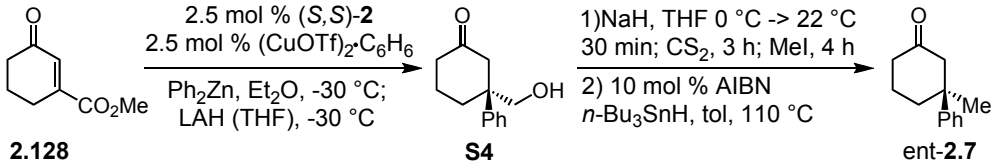


#	Time	Area	Height	Width	Area%
1	70.762	3848.5	42.3	1.5154	49.297
2	74.688	3958.2	56	1.1783	50.703



#	Time	Area	Height	Width	Area%
1	69.606	213.5	3.2	1.1166	3.871
2	74.713	5302.7	64	1.3818	96.129

Proof of absolute stereochemistry: The following sequence was carried out in order to obtain enantiomerically enriched material *ent*-**2.7**.



2.128 **S4** ent-**2.7**

An oven-dried 13x100 mm test tube was charged with **Ag-III** (3.02 mg, 2.50 μmol), $(CuOTf)_2 \bullet C_6H_6$ (1.3 mg, 2.50 μmol), and Ph_2Zn (65.7 mg, 0.300 mmol), weighed out under a N_2 atmosphere in a glove box. The test tube was sealed with a septum and wrapped with parafilm prior to removal from the glove box. The test tube containing the solids was allowed to cool to –30 °C (dry ice/acetone bath) and Et_2O (1.0 mL) was added through a syringe. The resulting mixture was allowed to stir for 10 minutes. (During this time the mixture became dark brown.) At this time, methyl 3-oxocyclohex-1-enecarboxylate (13.4 μL, 15.4 mg, 0.100 mmol) was added to the mixture through a syringe. After 42 h at –30 °C, $LiAlH_4$ (18.9 mg, 0.500 mmol) was added as a solution in THF (500 μL) via cannula. After 10 minutes at –30 °C, the reaction was quenched upon

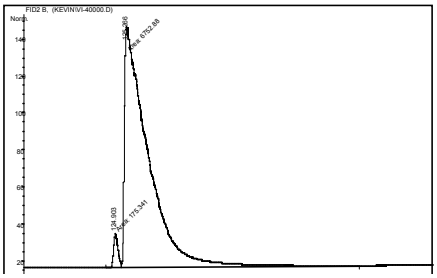
addition of a saturated aqueous solution of sodium potassium tartrate (5 mL) and diluted with CH_2Cl_2 (5 mL). The mixture was allowed to warm to 22 ^oC and stir for 2 h before it was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to afford a clear oil. The clear oil was purified by silica gel chromatography (10% Et_2O/hexanes) to yield 9.6 mg of an inseparable mixture of desired product (**S4**) and an unidentified compound (~25%). The mixture was carried on in the subsequent transformation.

Note: The following procedures are unoptimized. To a suspension of NaH (2.2 mg, 0.037 mmol, 60% dispersion in mineral oil) in THF (250 μL) at 0 ^oC was added **S4** (7.0 mg, 0.034 mmol) dissolved in THF (250 μL) via cannula. The mixture was allowed to warm to 22 ^oC and stir for 1 h. At this time, CS_2 (8.2 μL, 0.14 mmol) was added to the mixture through a syringe resulting in a yellow solution. The mixture was allowed to stir for 3 h until MeI (6.7 mL, 0.11 mmol) was added through a syringe. After 30 min, the reaction was quenched upon addition of H_2O (1 mL) and washed with $CHCl_3$ (2 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated, resulting in a yellow solid that was purified by silica gel chromatography (10% Et_2O/petroleum ether -> 30% Et_2O/petroleum ether) to afford 2.6 mg of the desired xanthate contaminated with minor impurities. This material was carried on in the subsequent transformation.

2,2'-Azobisisobutyronitrile (0.10 mg, 0.84 μmol) was added to the xanthate (2.6 mg, .0084 mmol) and Bu_3SnH (5.6 mL, 0.21 mmol) dissolved in toluene (250 μL) in a screw cap vial. The vial was sealed with a cap and allowed to stir at 110 ^oC. After 1 h,

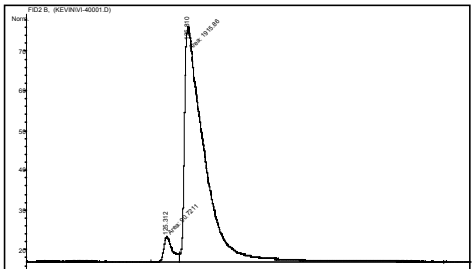
the mixture was allowed to cool to 22 °C and was passed through a short plug of silica gel (4 cm x 1 cm) eluted with 50% Et_2O/petroleum ether. The volatiles were removed in vacuo, resulting in a clear oil that was purified by silica gel chromatography (25% Et_2O/petroleum ether) to afford ent-**2.7** as a colorless oil. The ^1H NMR spectrum of ent-**2.7** was identical to previously reported data (see above). Based on the retention times from GLC chromatograms (illustrated below) of *ent*-**2.7** derived from reaction presented in Scheme 2.22 (which was assigned *S* absolute stereochemistry) and **S4**, we assigned *R* absolute stereochemistry to **2.122**.

*ent-**2.7** From Reaction in Scheme 2.22*



#	Time	Area	Height	Width	Area (%)
1	124.903	175.3	18.8	0.1556	2.528
2	125.266	6752.9	129.8	0.8671	97.47

*ent-**2.7** From **S4***



#	Time	Area	Height	Width	Area (%)
1	125.312	90.7	6.5	0.2326	4.520
2	125.81	1915.9	59.2	0.5391	95.48

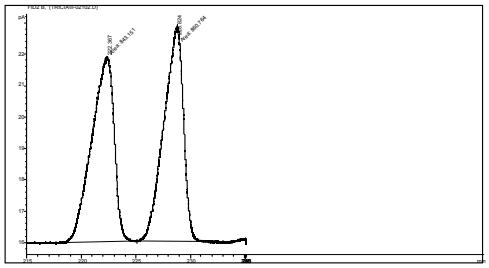
(*R*)-*tert*-Butyl-1-methyl-3-oxocyclohexanecarboxylate (2.112). IR (neat): 2978 (m), 2941 (m), 2884 (w), 1737 (s), 1469 (m), 1379 (m), 1327 (m), 1264 (m), 1232 (m), 1158 (s), 1132 (s), 848 (w); **^1H NMR ($CDCl_3$, 400 MHz):** δ 2.67 (1H, dt, *J* = 14.4, 2.0 Hz, C(O)C**H**HC), 2.39-2.31 (1H, m, $CH_2CH_2CH_2C(O)$), 2.20 (1H, dddd, *J* = 16.0, 9.6, 6.4, 1.2 Hz), 2.11-2.05 (2H, m, C(O)CH**H**C and $CH_2CH_2CH_2C(O)$), 1.95-1.86 (1H, m, $CH_2CH_2CH_2C(O)$), 1.82-1.68 (1H, m, $CH_2CH_2CH_2C(O)$), 1.63 (1H, ddd, *J* = 14.0, 10.4,

4.0 Hz, $CH_2CH_2CH_2C(O)$), 1.42 (9H, s, $C(CH_3)_3$), 1.21 (3H, s, CH_3); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 209.6, 175.3, 81.3, 50.3, 47.1, 40.3, 34.9, 28.1, 25.2, 22.3; **HRMS (CI+):** Calcd for $C_{12}H_{21}O_3$: 213.149070 [M^++H], Found: 213.149254; **Optical Rotation:** $[\alpha]_D^{20}$ –19.6 (*c* 1.25, $CHCl_3$) for an enantiomerically enriched sample of 85% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (β-dex column, 15 psi, 140 °C, t_{major} = 19.98 min, t_{minor} = 20.25 min).

(*R*)-*tert*-Butyl-3-oxo-1-phenylcyclohexanecarboxylate (1.123). IR (neat): 3062 (w), 2974 (w), 2936 (w), 2873 (w), 2363 (w), 2326 (w), 1722 (s), 1451 (m), 1369 (m), 1250 (m), 1162 (m), 1149 (m), 1111 (w), 847 (w), 771 (w), 696 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33–7.30 (4H, m, Ar**H**), 7.25-7.23 (1H, m, Ar**H**), 3.00 (1H, dd, *J* = 13.2, 1.6 Hz, C(O)CH**H**C), 2.62 (1H, d, *J* = 15.2 Hz, C(O)C**H**HC), 2.52-2.49 (1H, m, CC**H**HCH_2), 2.43-2.36 (1H, m, CCH**H**CH_2), 2.28-2.23 (2H, m, C(O)CH_2CH_2), 1.86-1.78 (2H, m, $CH_2CH_2CH_2$), 1.34 (9H, s, $C(CH_3)_3$); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 209.1, 175.3, 142.1, 128.8, 127.3, 126.0, 81.8, 54.6, 49.9, 40.5, 33.2, 27.9, 21.7; **HRMS (CI+):** Calcd for $C_{17}H_{23}O_3$: 275.1647 [M^++H], Found 275.1653; **Optical Rotation:** $[\alpha]_D^{20}$ -5.3 (*c* 0.75, $CHCl_3$) for an enantiomerically enriched sample of 79% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (74% ee shown; chiral dex GTA column, 15 psi, 120 °C).



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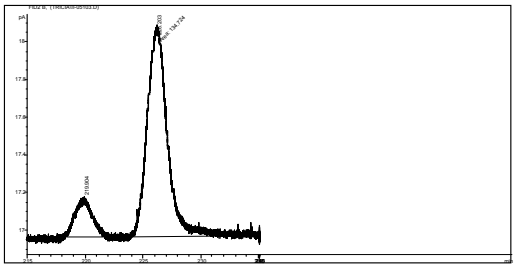
2	228.824	860.8	6.9	2.0875	50.517

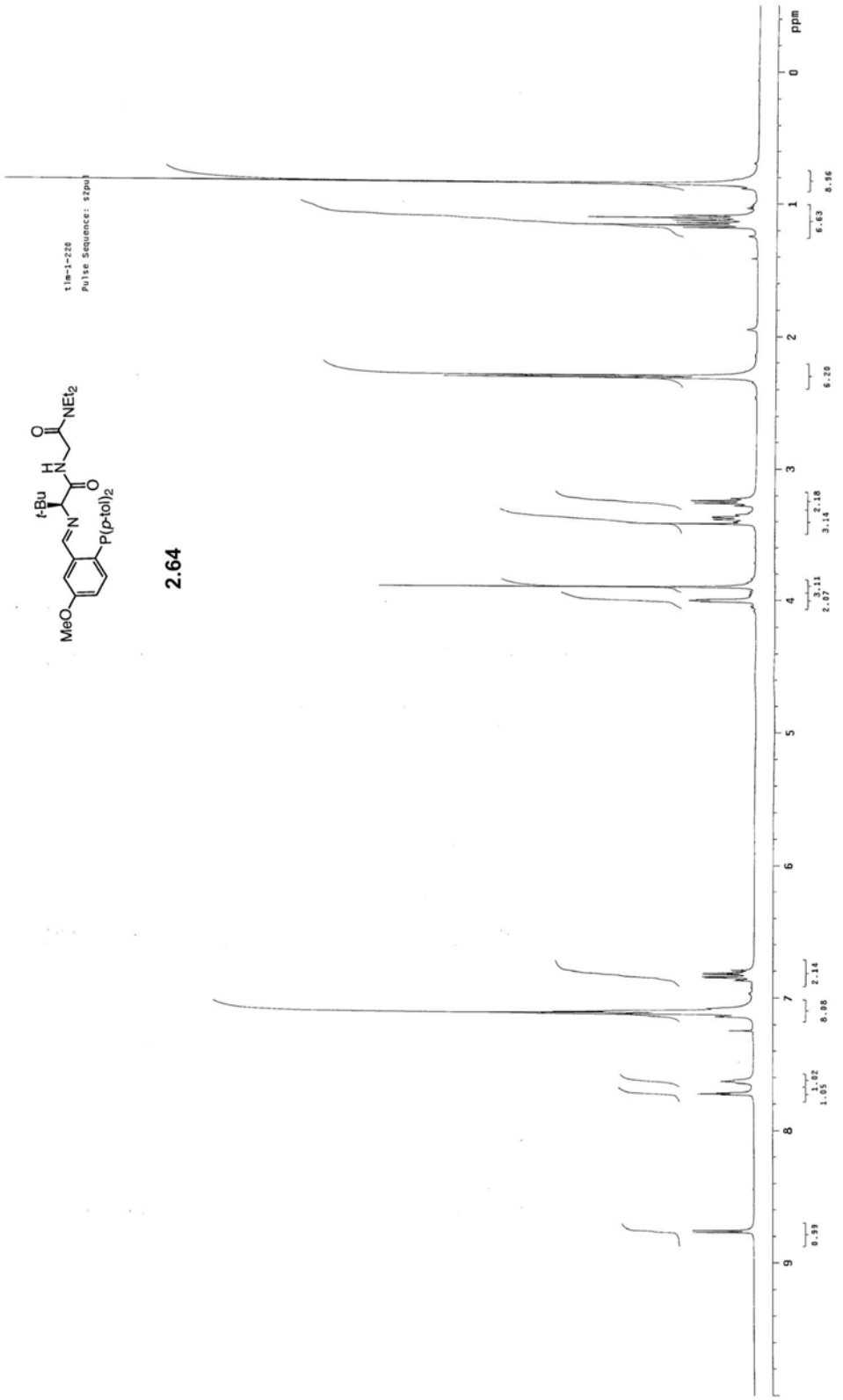


#	Time	Area	Height	Width	Area (%)
1	219.904	20.1	2.1E-1	1.5757	13.000
2	226.203	134.7	1.1	2.0044	87.000

■ **Experimental procedure for Cu-catalyzed conjugate addition of *Me_2Zn* to cyclic unsaturated γ-ketoester 2.128 and in situ reduction with $LiAlH_4$**

(*R*)-3-(hydroxymethyl)-3-methylcyclohexanone (2.129). An oven-dried 13x100 mm test tube was charged with **Ag-III** (3.02 mg, 2.50 μmol) and $(CuOTf)_2 \bullet C_6H_6$ (1.30 mg, 2.50 μmol), weighed out under a N_2 atmosphere in a glove box. The test tube was sealed with a septum and wrapped with parafilm before removal from the glove box. *tert*-Butylmethylether (1.0 mL) was added through a syringe and the resulting solution was allowed to stir for five minutes before cooling to –78 ºC (dry ice/acetone bath). Dimethylzinc (21.0 μL, 0.300 mmol) (PYROPHORIC, USE EXTREME CAUTION) was added and the resulting light yellow mixture was allowed to warm to –30 ºC (cryocool). (During this time the mixture became dark brown.) After 10 minutes at –30 ^oC, methyl 3-oxocyclohex-1-enecarboxylate (13.4 μL, 15.4 mg, 0.100 mmol) was added to the mixture through a syringe. After 15 h at –30 ^oC, $LiAlH_4$ (4.00 mg, 0.100 mmol) dissolved in THF (1.0 mL) was added to the mixture via cannula. The solution was allowed to warm to 0 ºC and stir for 6 h at which time the reaction was quenched upon

addition of a saturated aqueous solution of sodium potassium tartrate (2.0 mL) and diluted with CH_2Cl_2 (2.0 mL). The resulting mixture was allowed to warm to 22 ºC and stir for 2 h, after which time the reaction was washed with CH_2Cl_2 (4 x 2 mL). The combined organic layers were dried over $MgSO_4$ and filtered through filter paper. The volatiles were removed in vacuo resulting in a yellow oil, which was purified by silica gel column chromatography (50% Et_2O/petroleum ether) to afford 10.8 mg (0.0760 mmol, 76.0%) of the desired product as a clear oil. **IR (neat):** 3390 (br), 2955 (m), 2867 (m), 1703 (s), 1457 (w), 1420 (w), 1055 (m), 671 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.39 (1H, d, *J* = 11.6 Hz, CH**H**OH), 3.36 (1H, d, *J* = 12.4 Hz, C**H**HOH), 2.36 (1H, d, *J* = 13.6 Hz, C(O)CH**H**C), 2.32-2.23 (2H, m, C(O)C**H**$_2$CH$_2$), 2.06 (1H, dt, *J* = 13.6, 1.6 Hz, C(O)CH**H**C$_2$), 2.00-1.76 (3H, m, C(O)CH$_2$C**H**$_2$ and C(O)CH$_2$CH$_2$C**H**H), 1.52-1.47 (2H, m, CH$_2$O**H** and C(O)CH$_2$CH$_2$CH**H**), 0.92 (3H, s, C**H**$_3$); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 201.2, 71.3, 50.1, 41.1, 32.8, 22.6, 22.2, 10.6; **HRMS (EI+):** Calcd for $C_8H_{14}O_2$: 142.0994, Found 142.0944.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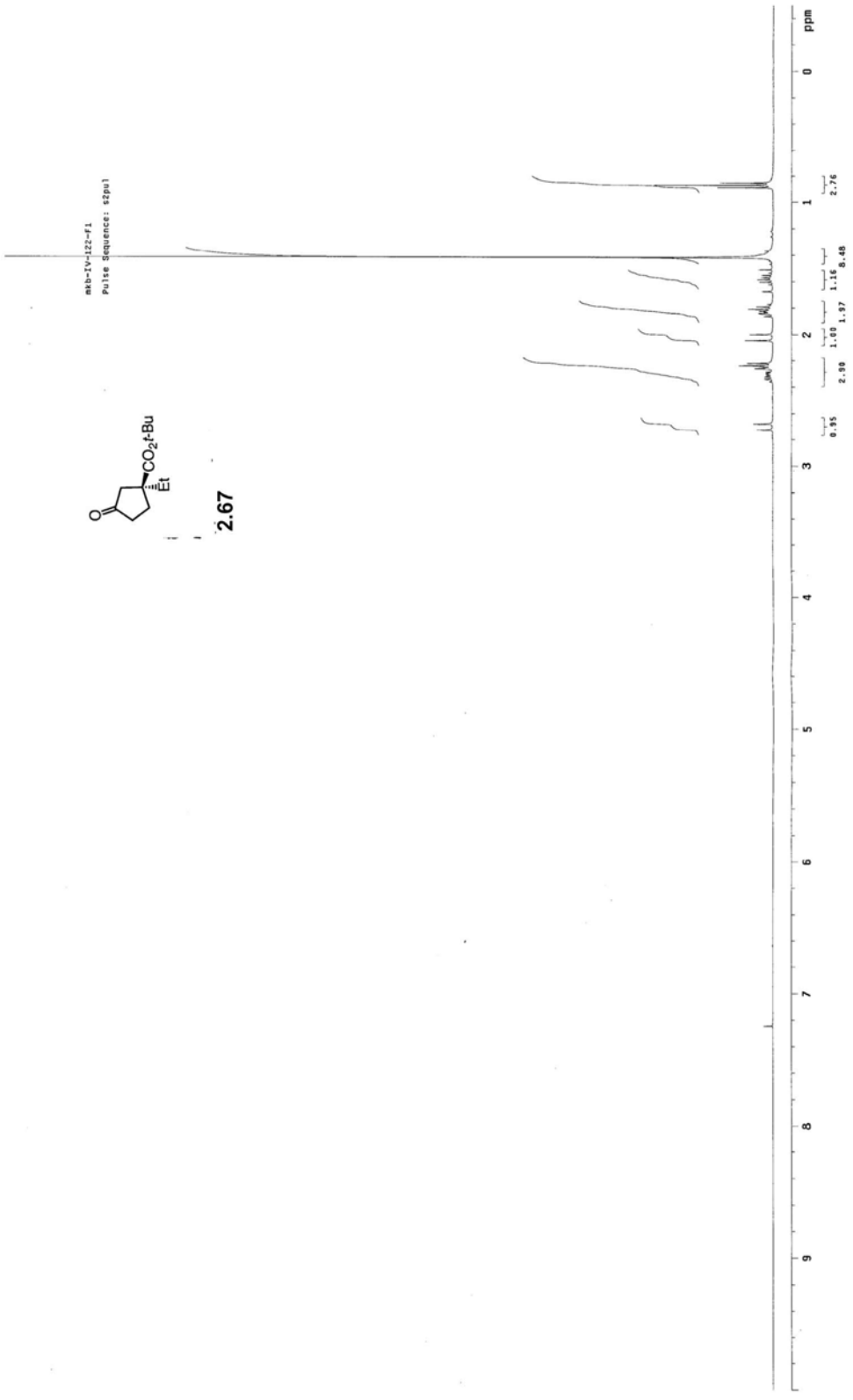
t-Bu
P(p-tol)2
MeO
2.64
ppm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Et
O
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ppm
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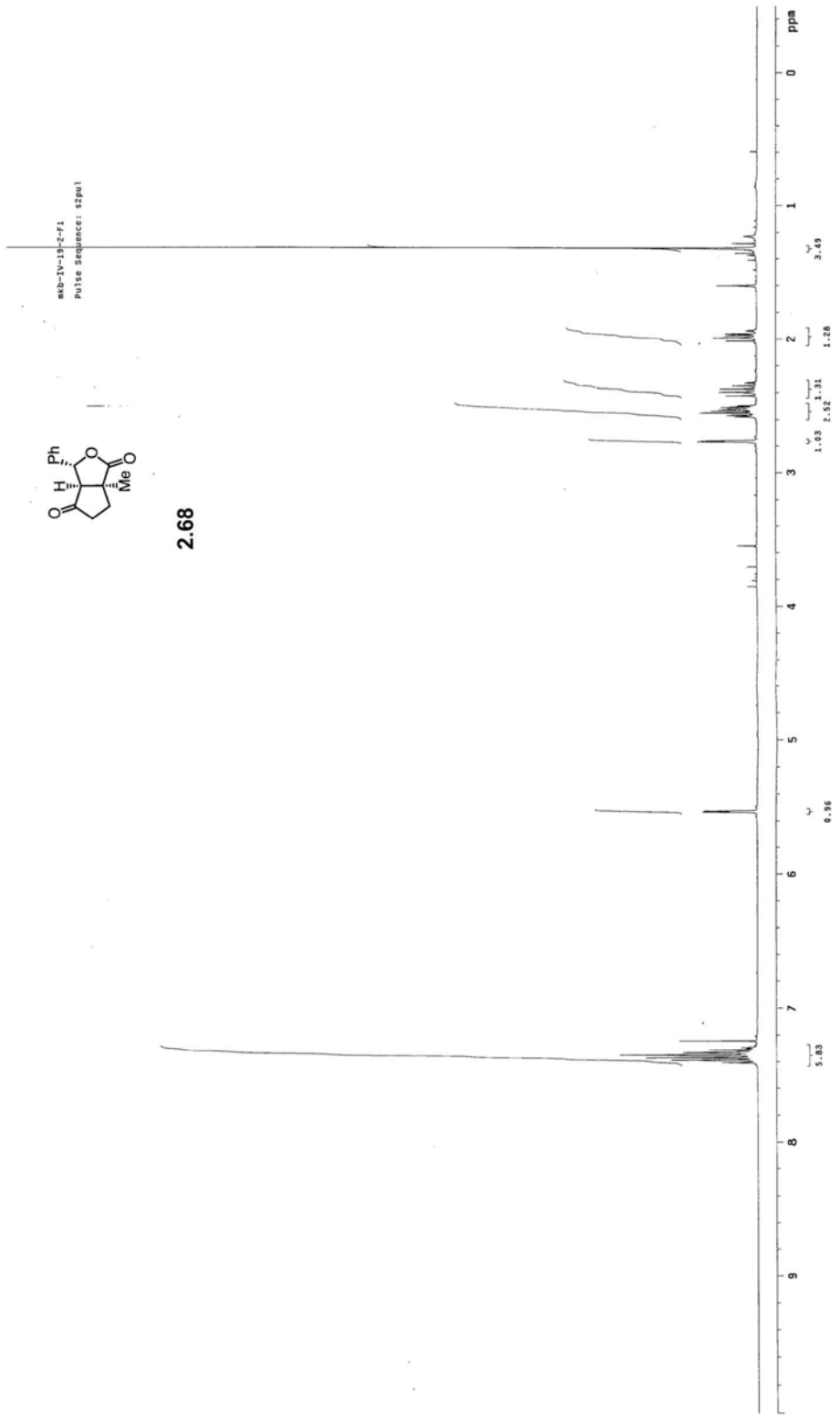
2.90
1.60
1.97
1.15
8.48
2.76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O
O
Me
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ppm
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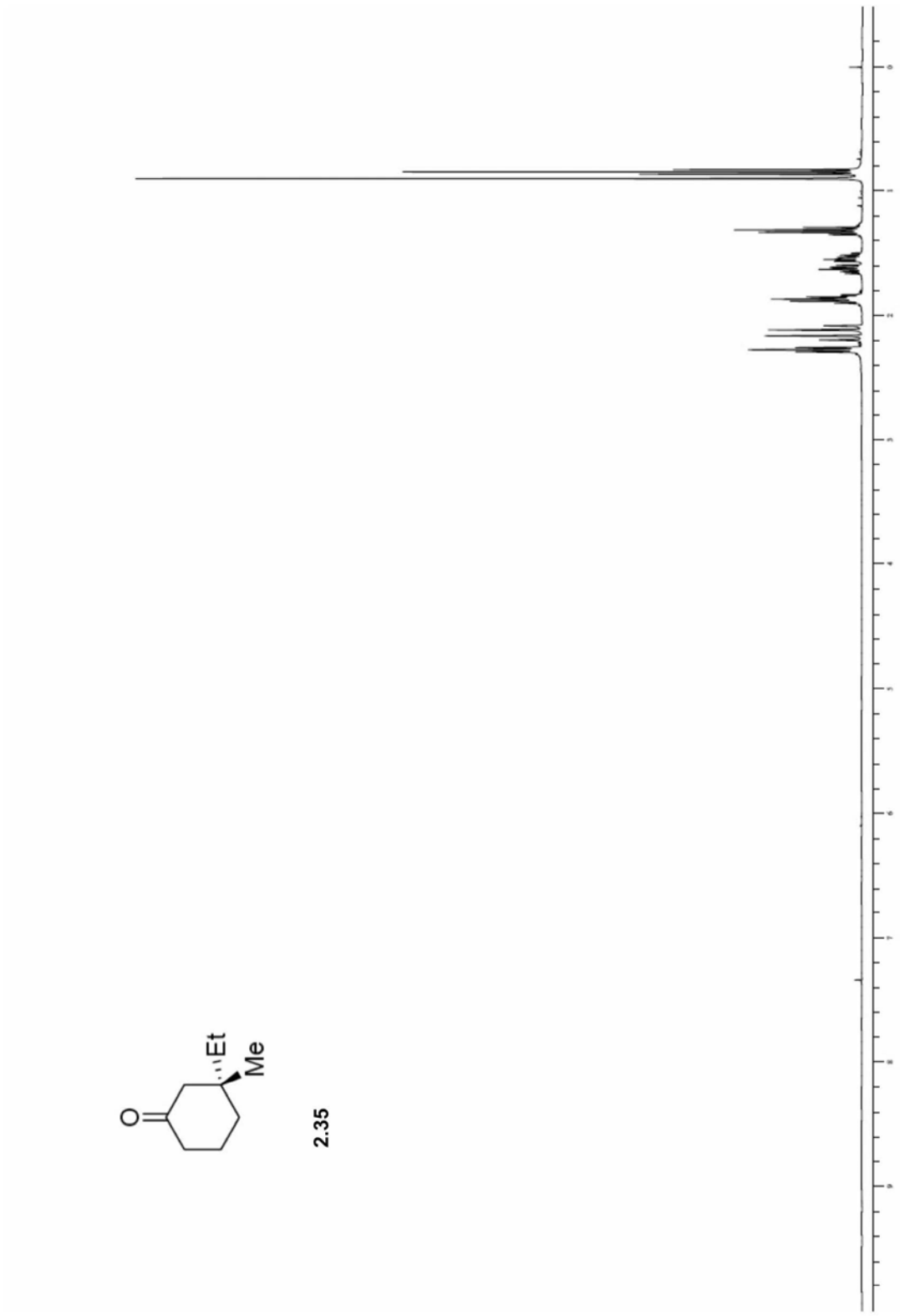
1.28
1.31
2.52
1.03
0.96
5.83



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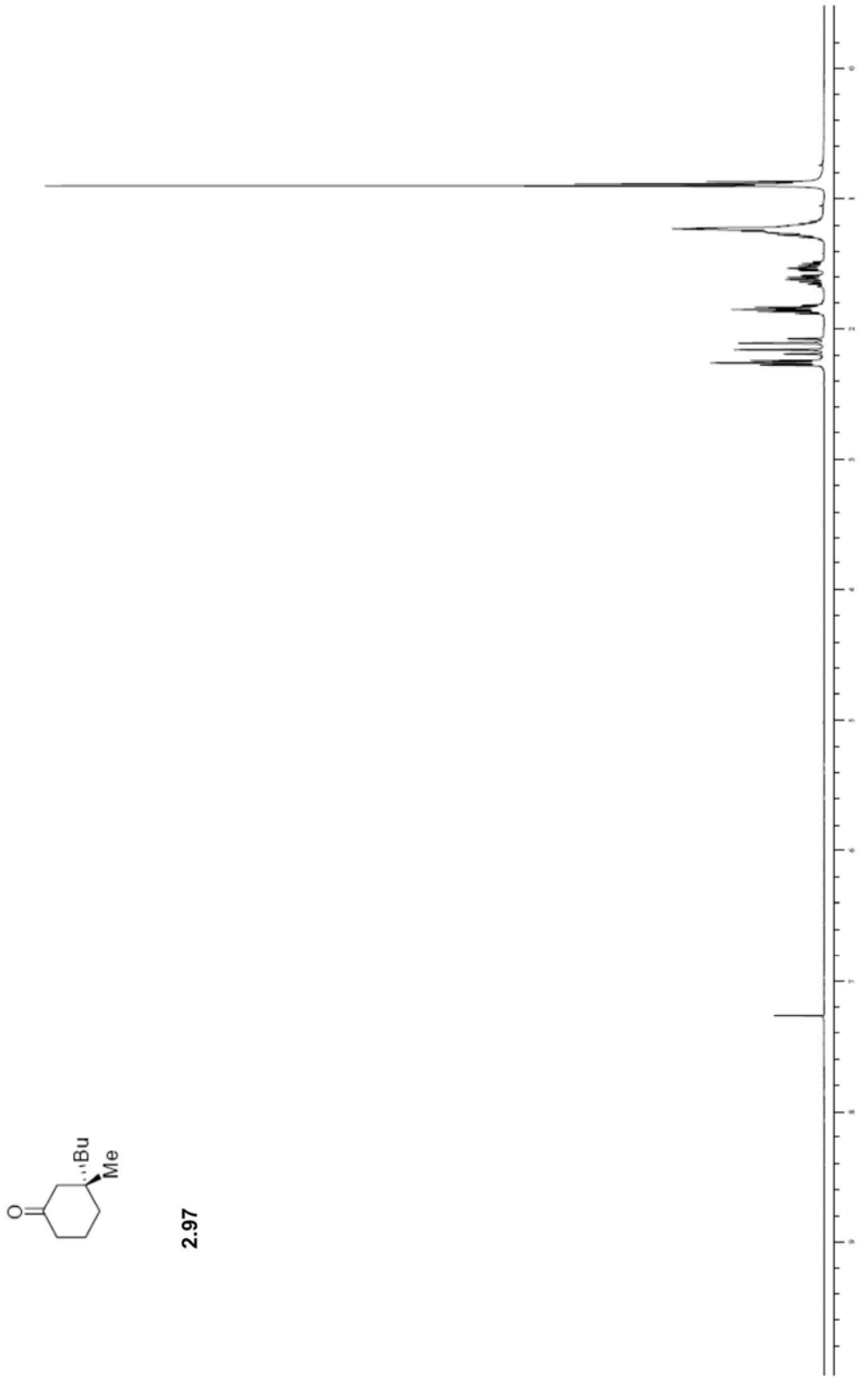

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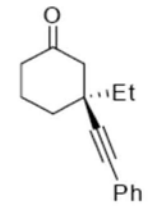
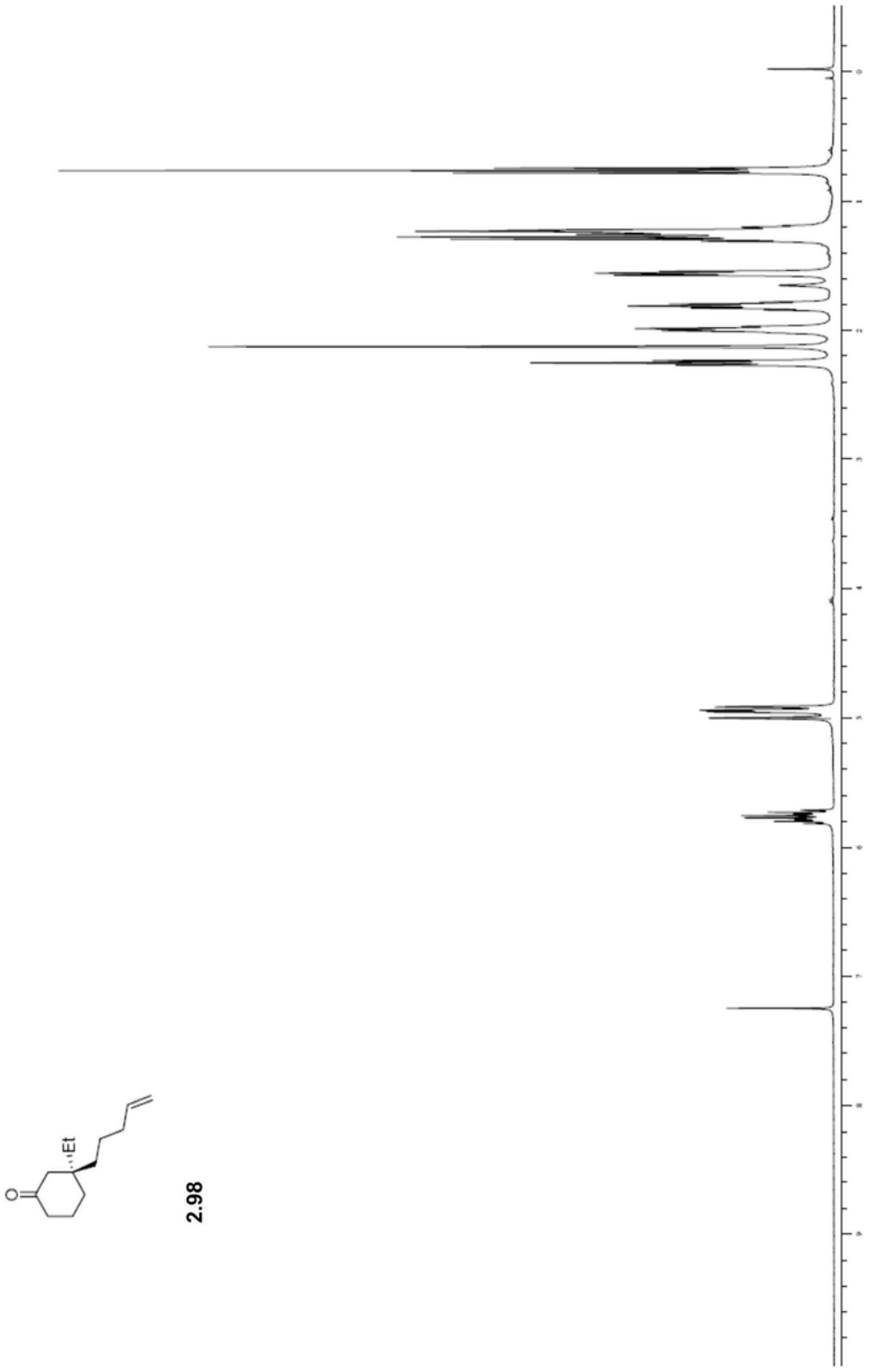


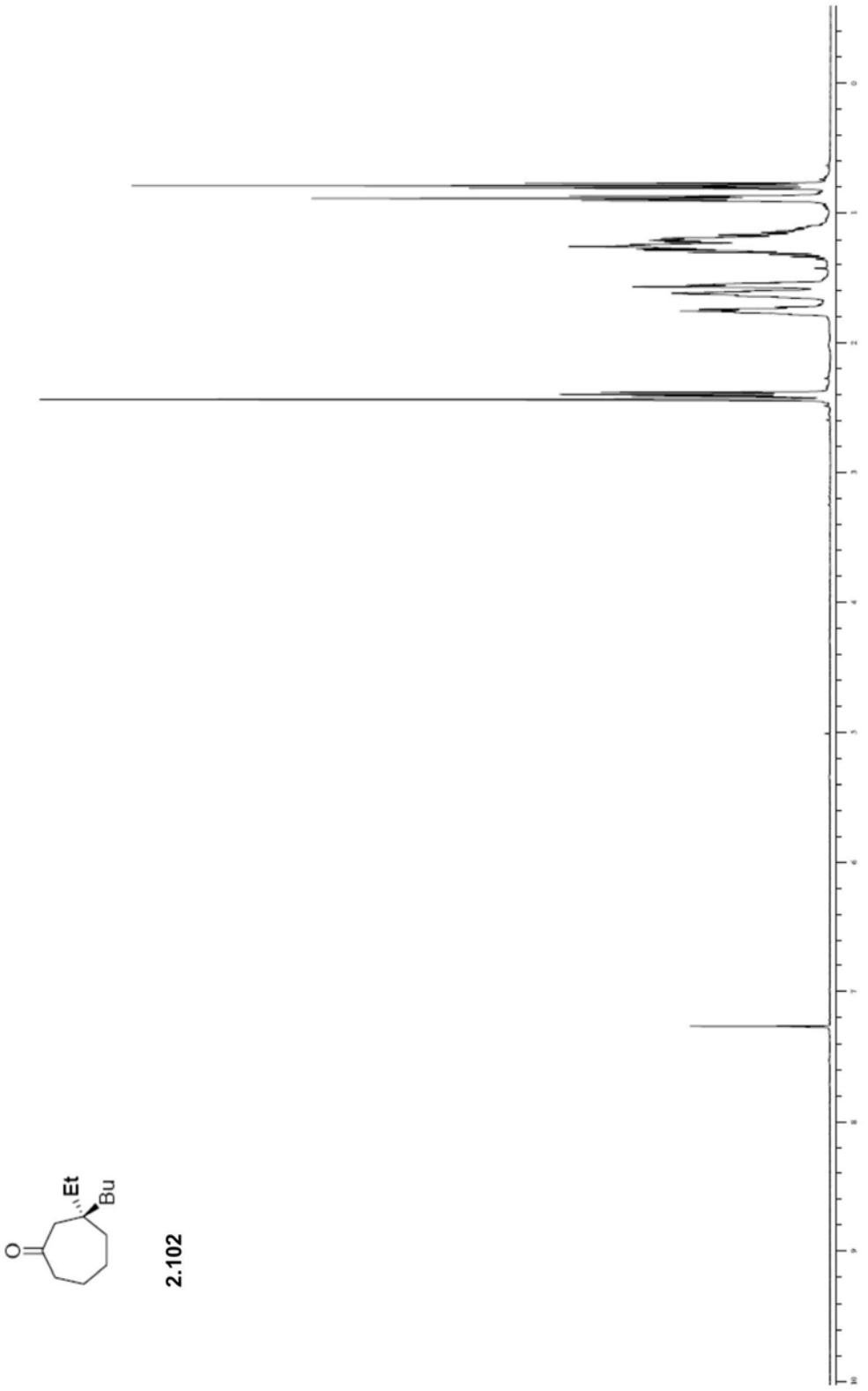
2.100



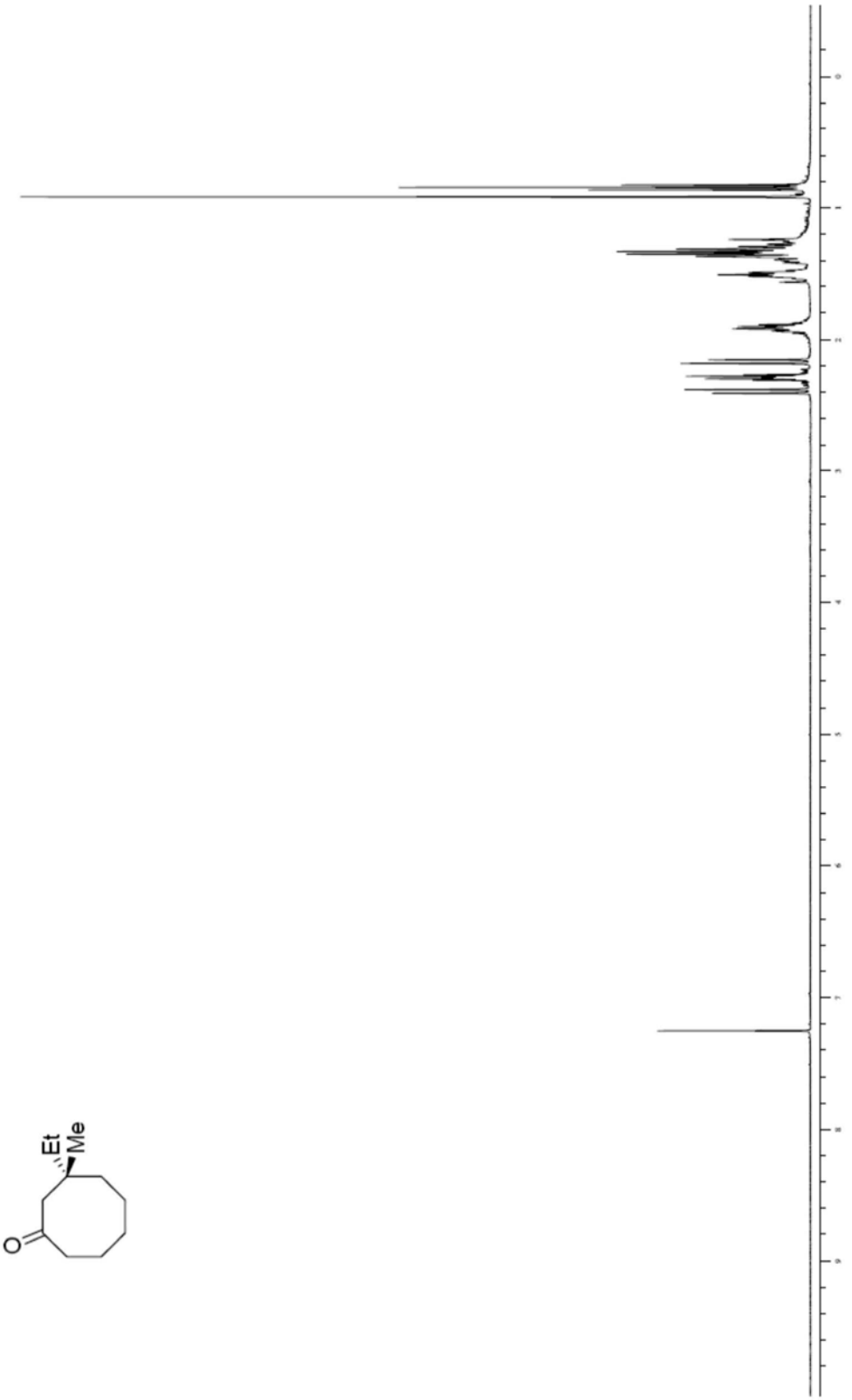
2.98

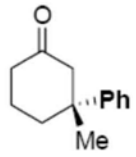
ent-2.5

2.101

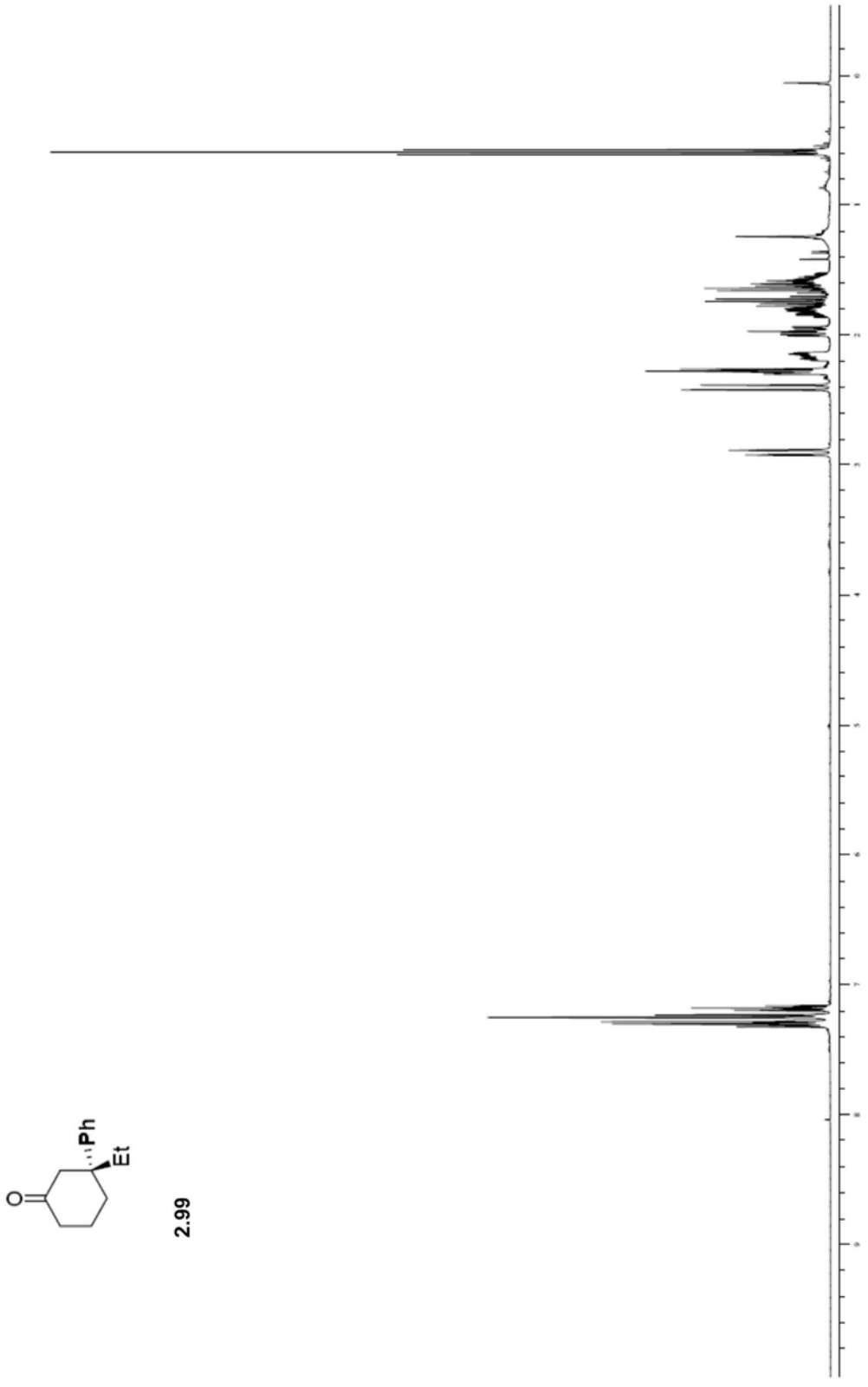


2.102


Et
Me
O



ent-2.7



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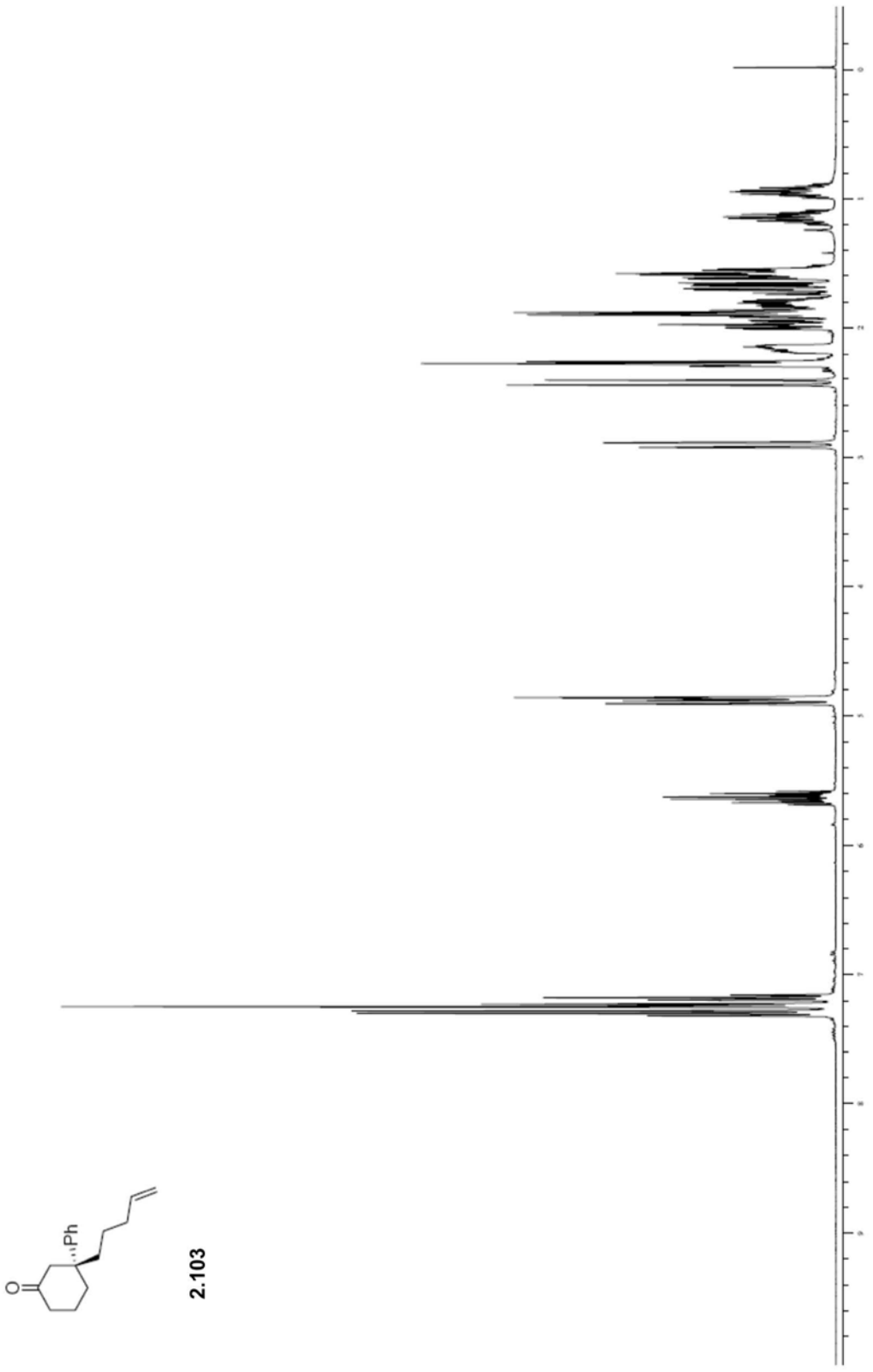

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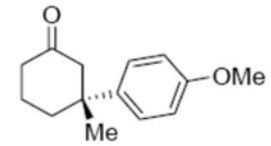
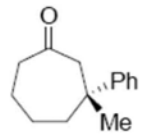


From 2.34



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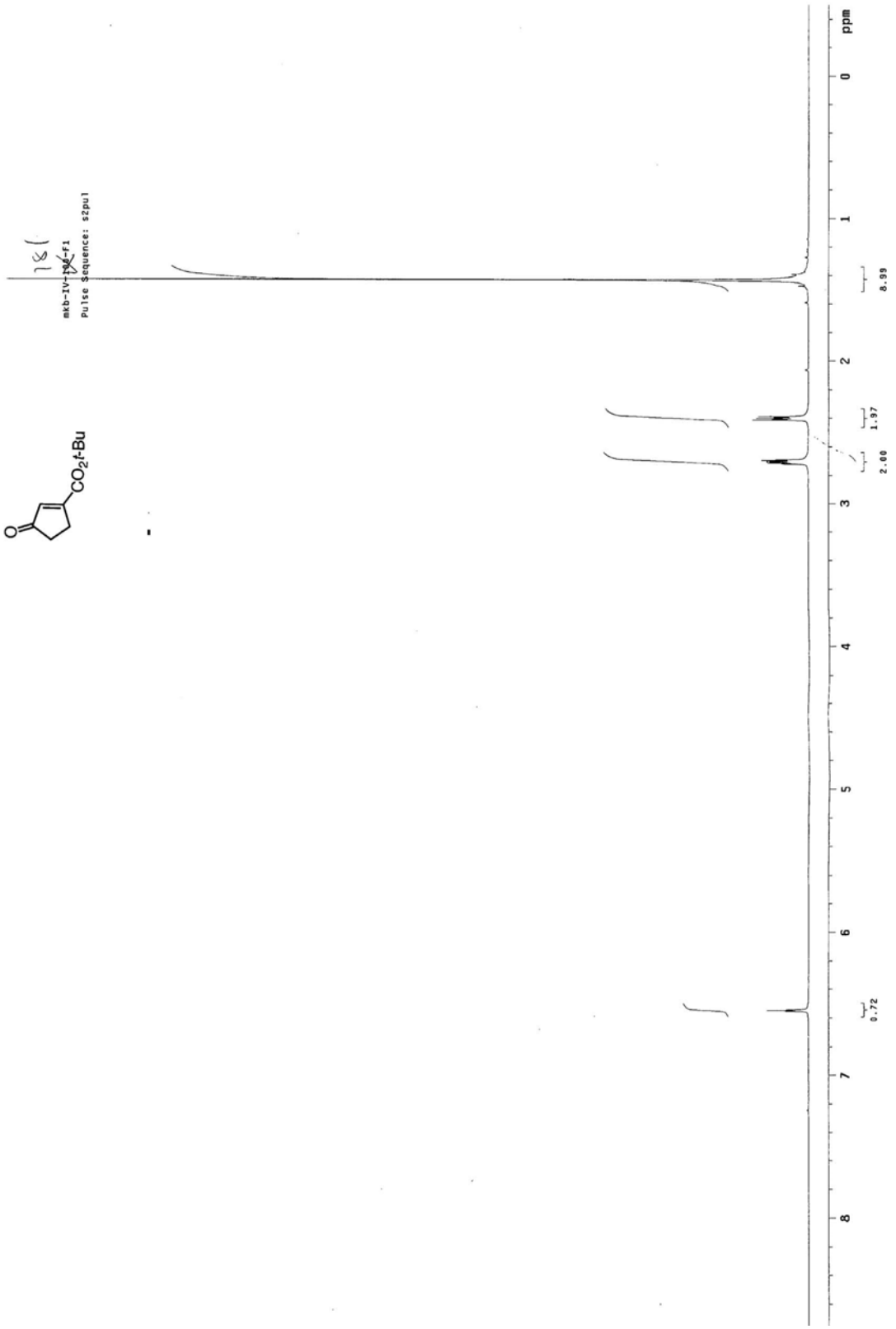
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ppm
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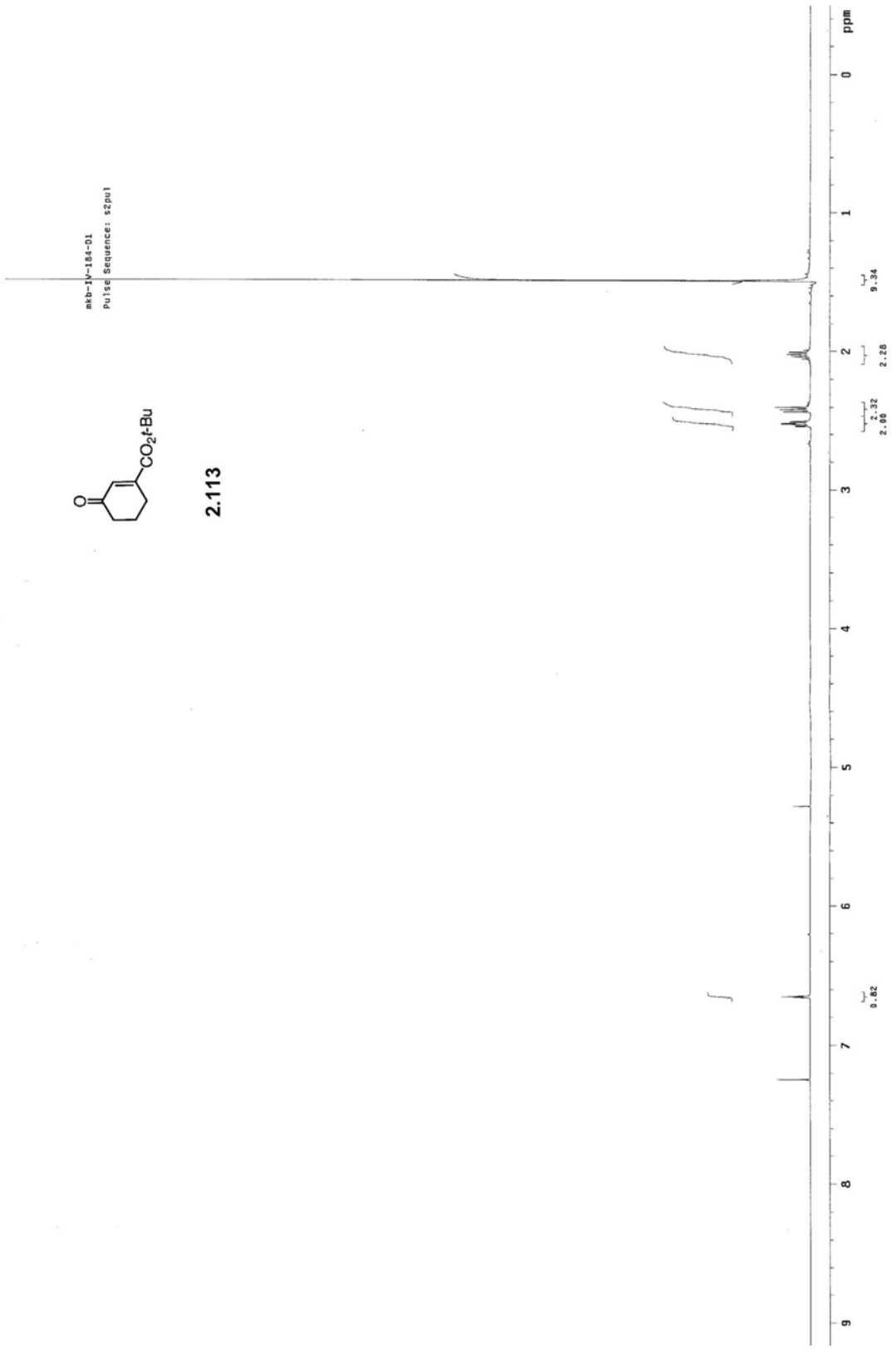
1.97
2.00
0.72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O
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ppm
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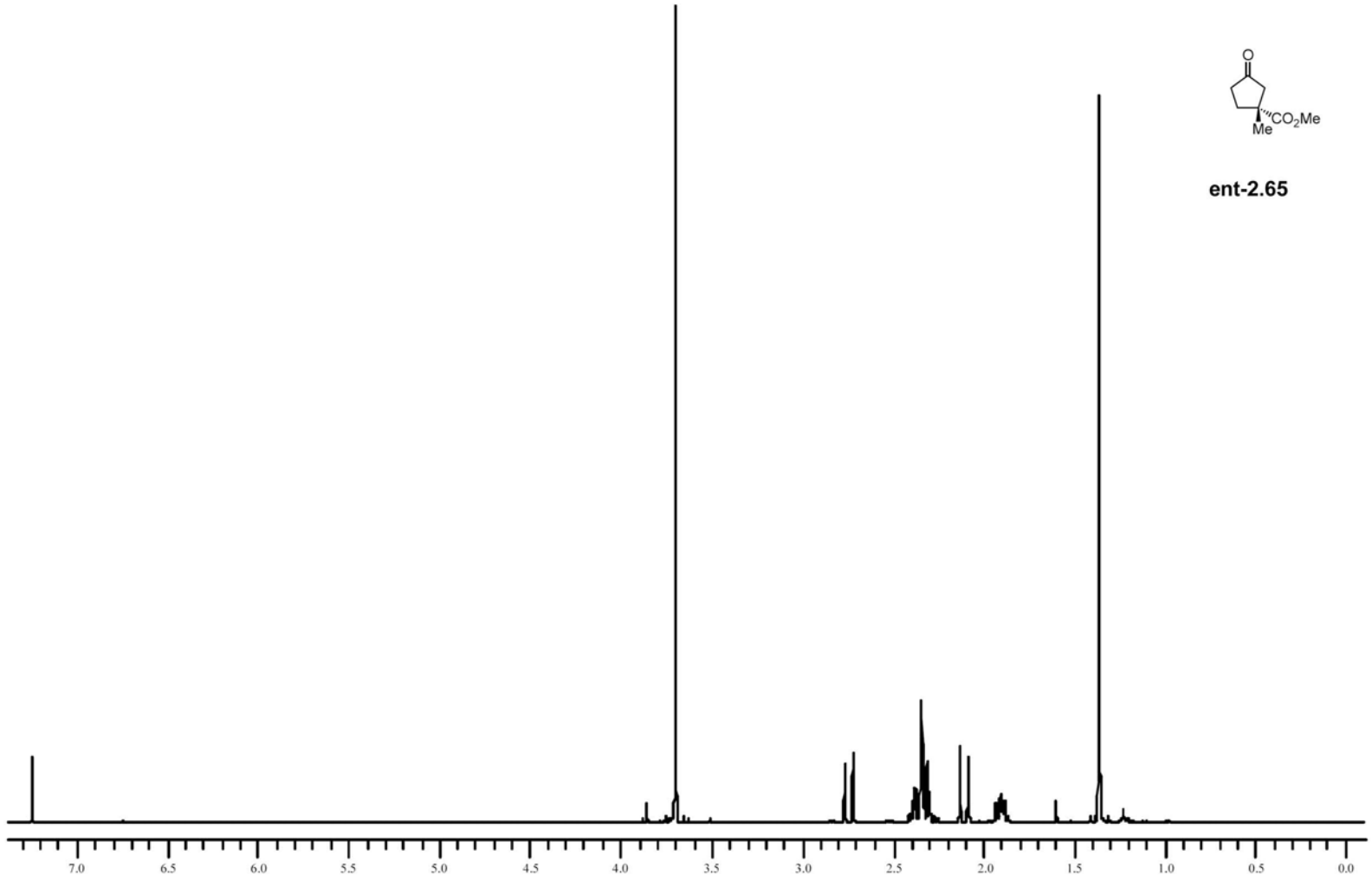
2
3
4
5
6
7
8
9
9.34
2.28
2.32
2.00
0.82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Me
ent-2.65
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6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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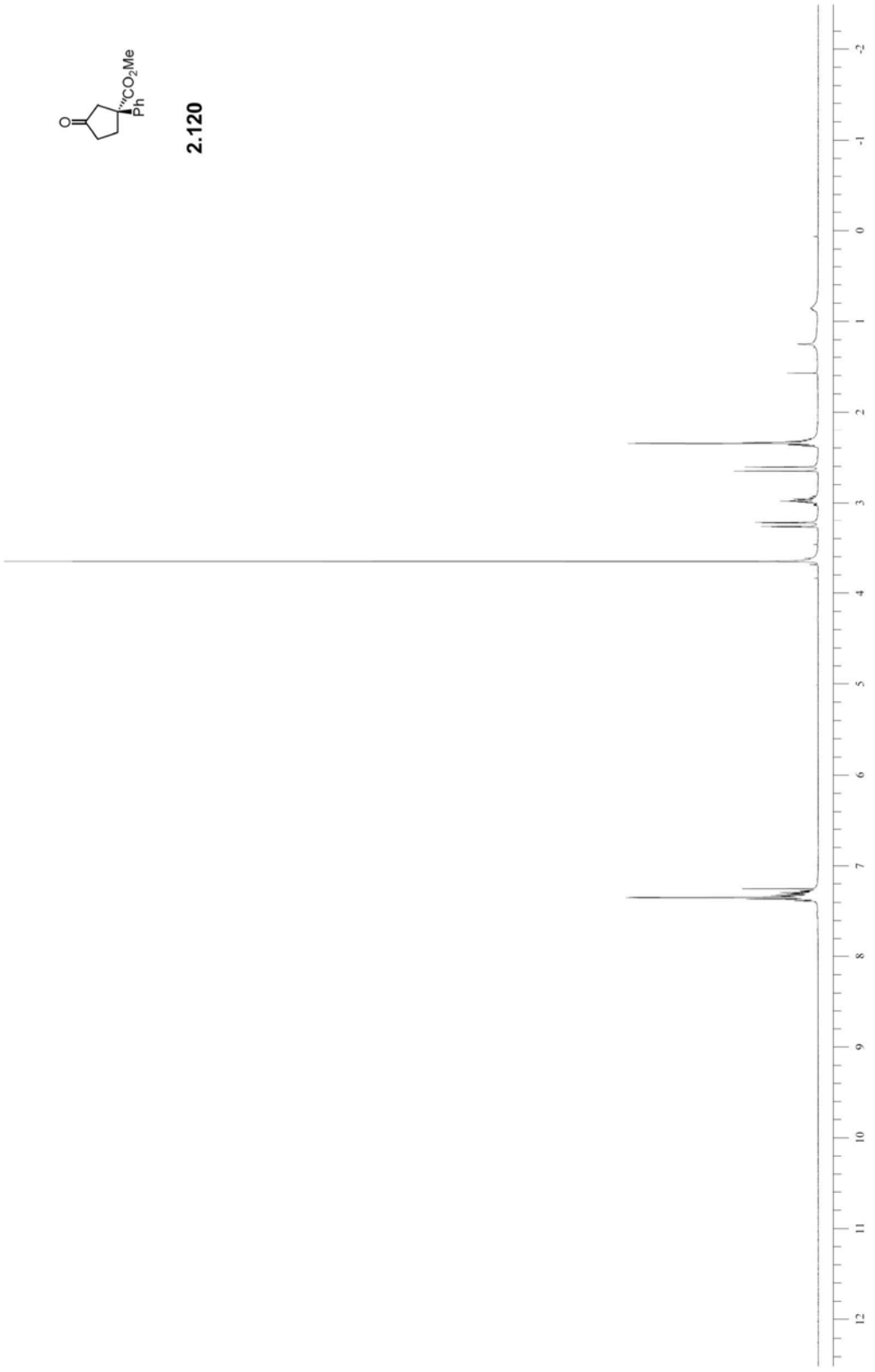
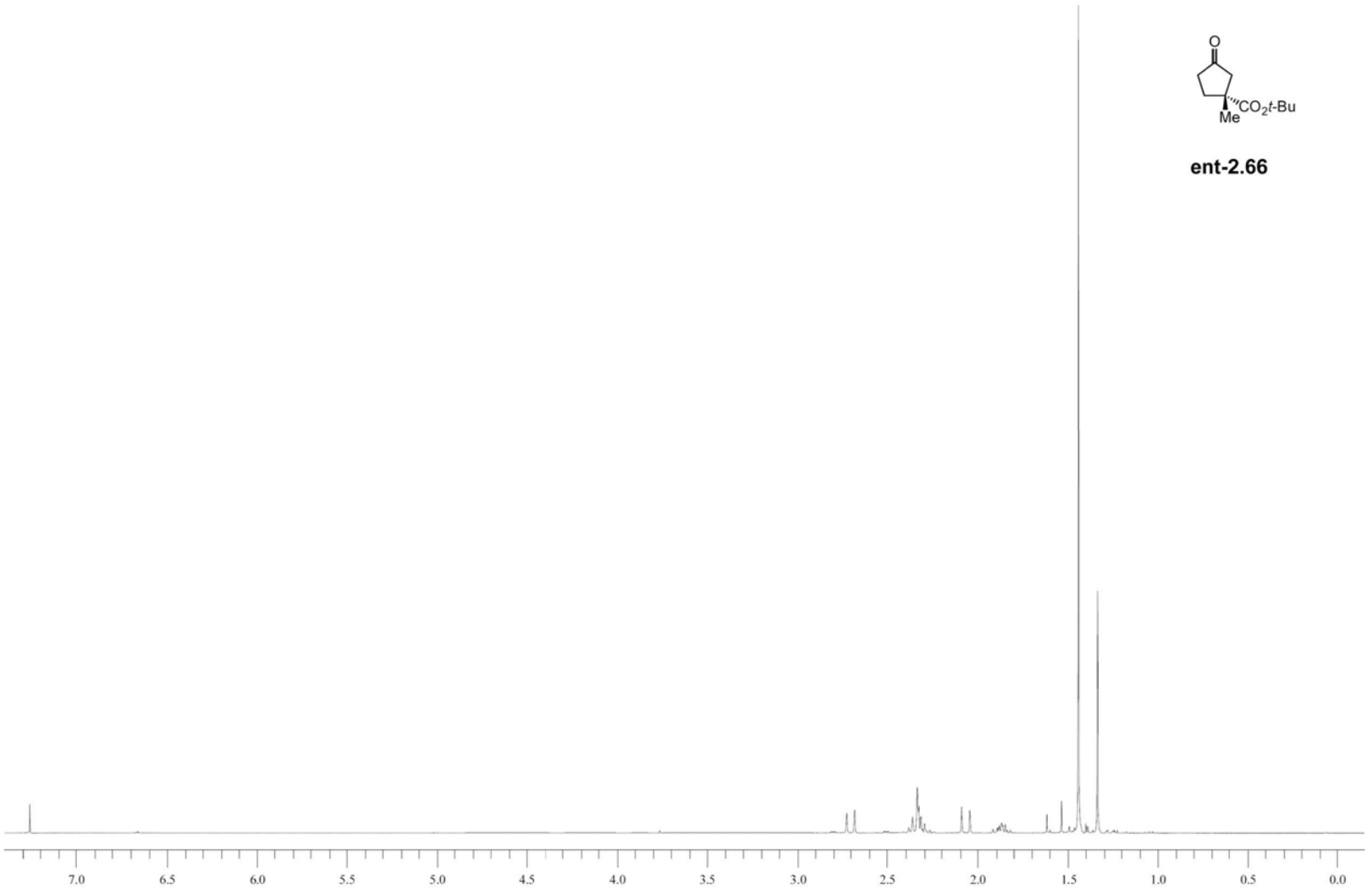
2.0
1.5
1.0
0.5
0.0

ent-2.57

2.114


O
Ph
CO2Me
2.120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Me
CO2t-Bu
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6.0
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4.5
4.0
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3.0
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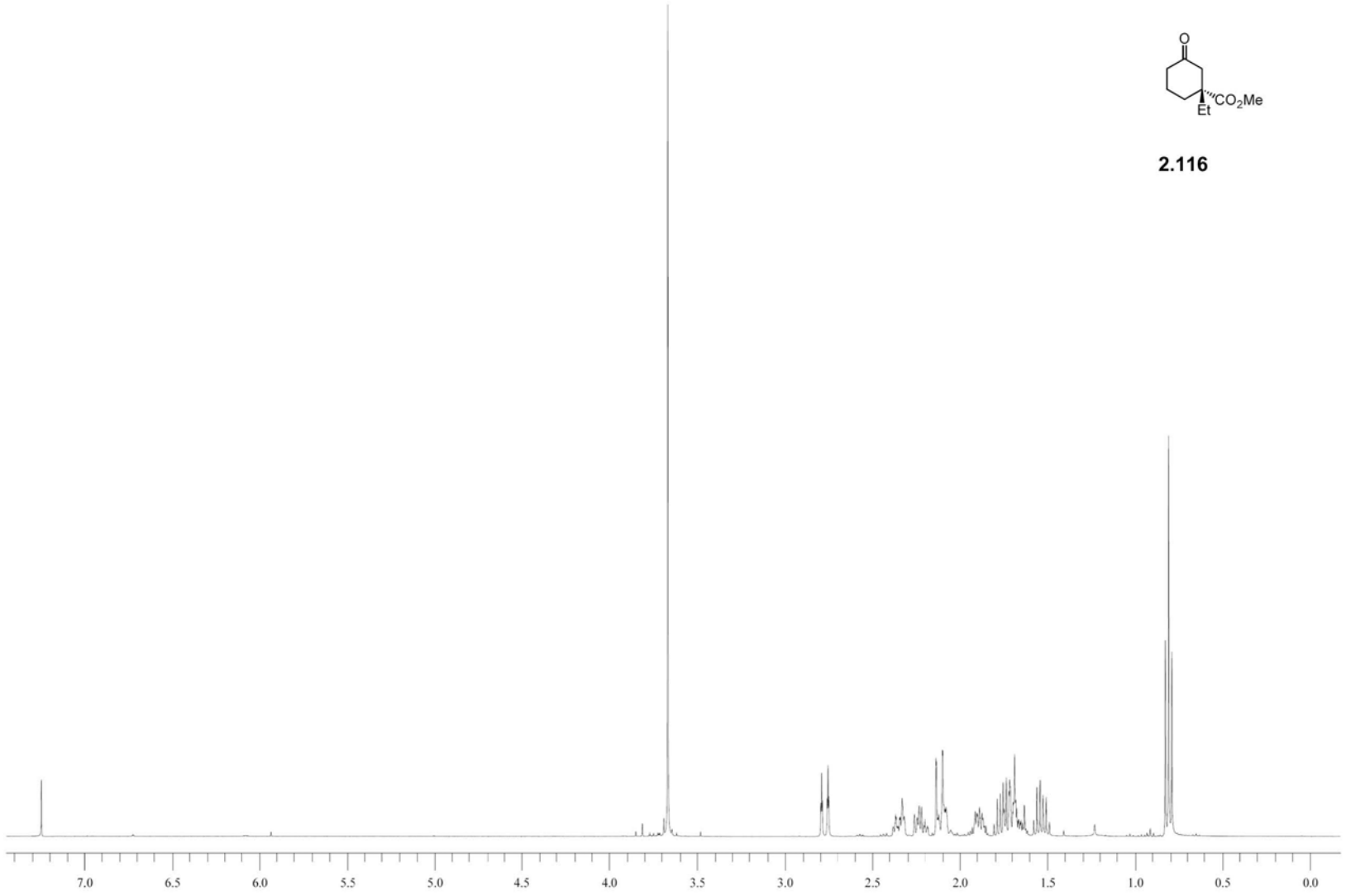
1.5
1.0
0.5
0.0

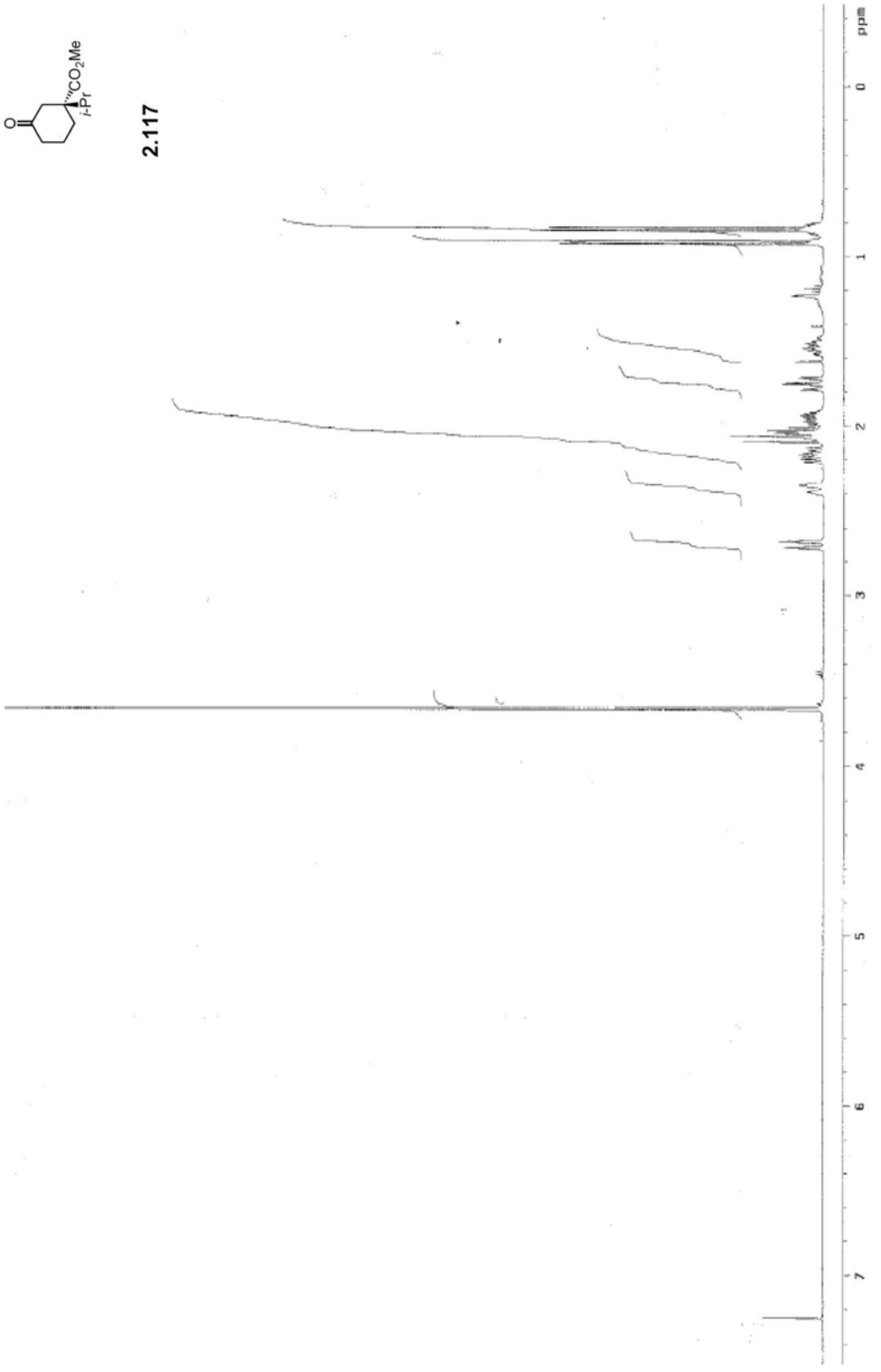
2.115

2.121

CO2Me
Me
2.111



2.116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2
3
4
5
6
7

Me
CO2t-Bu
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7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

2.122

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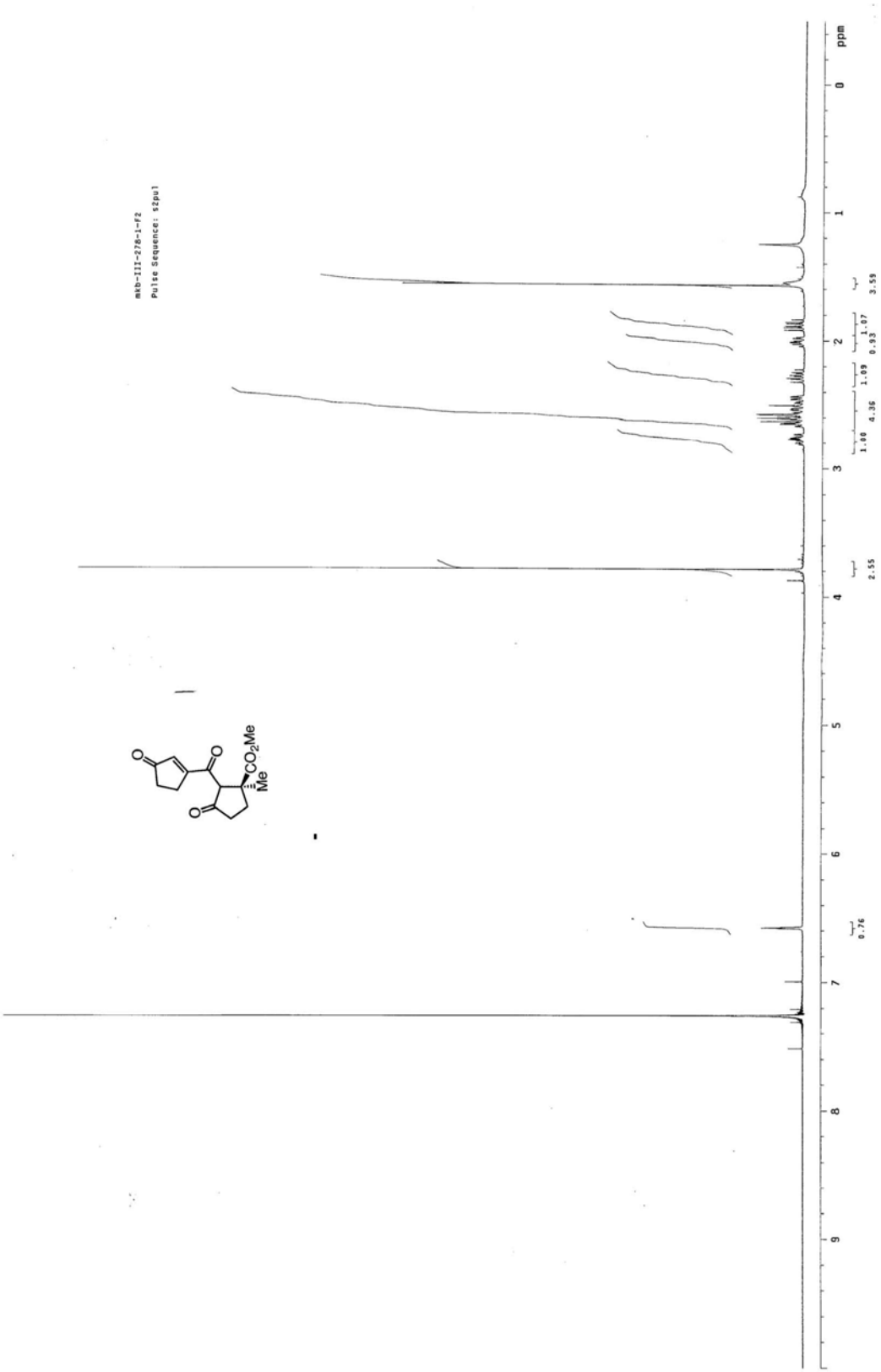
CO2t-Bu
Ph
2.123
ppm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1.07
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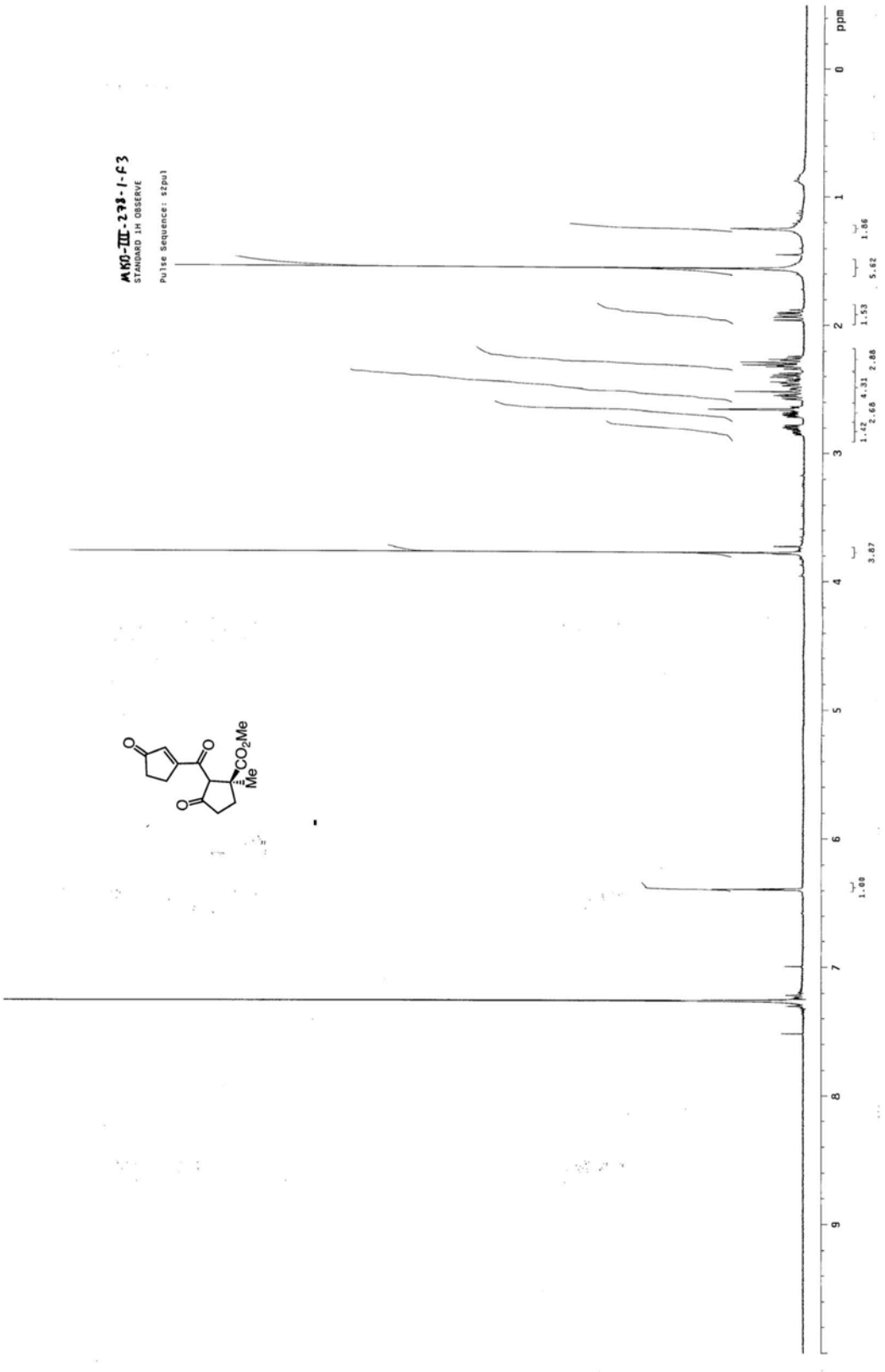
0.76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Pulse Sequence: s2pul
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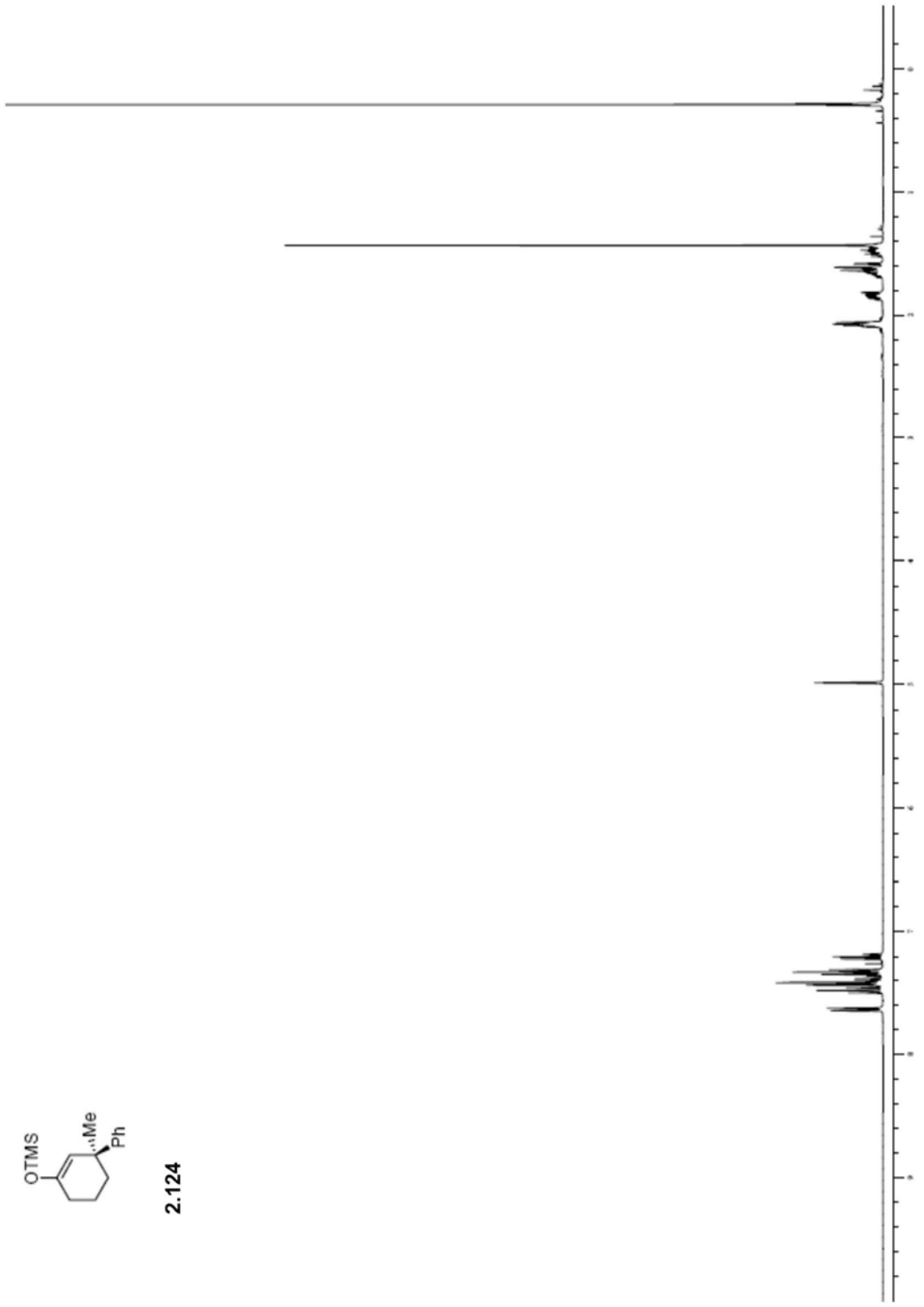
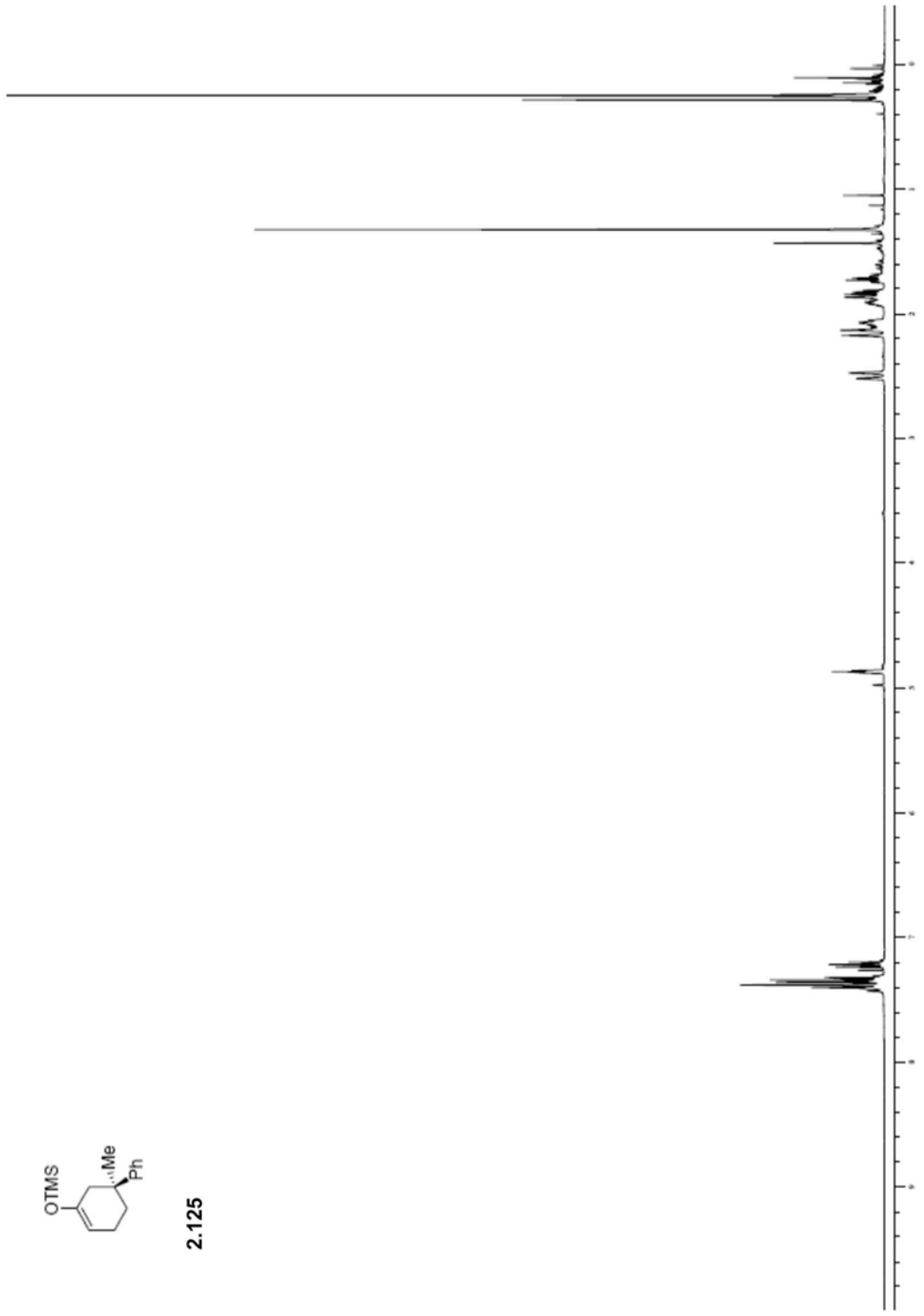
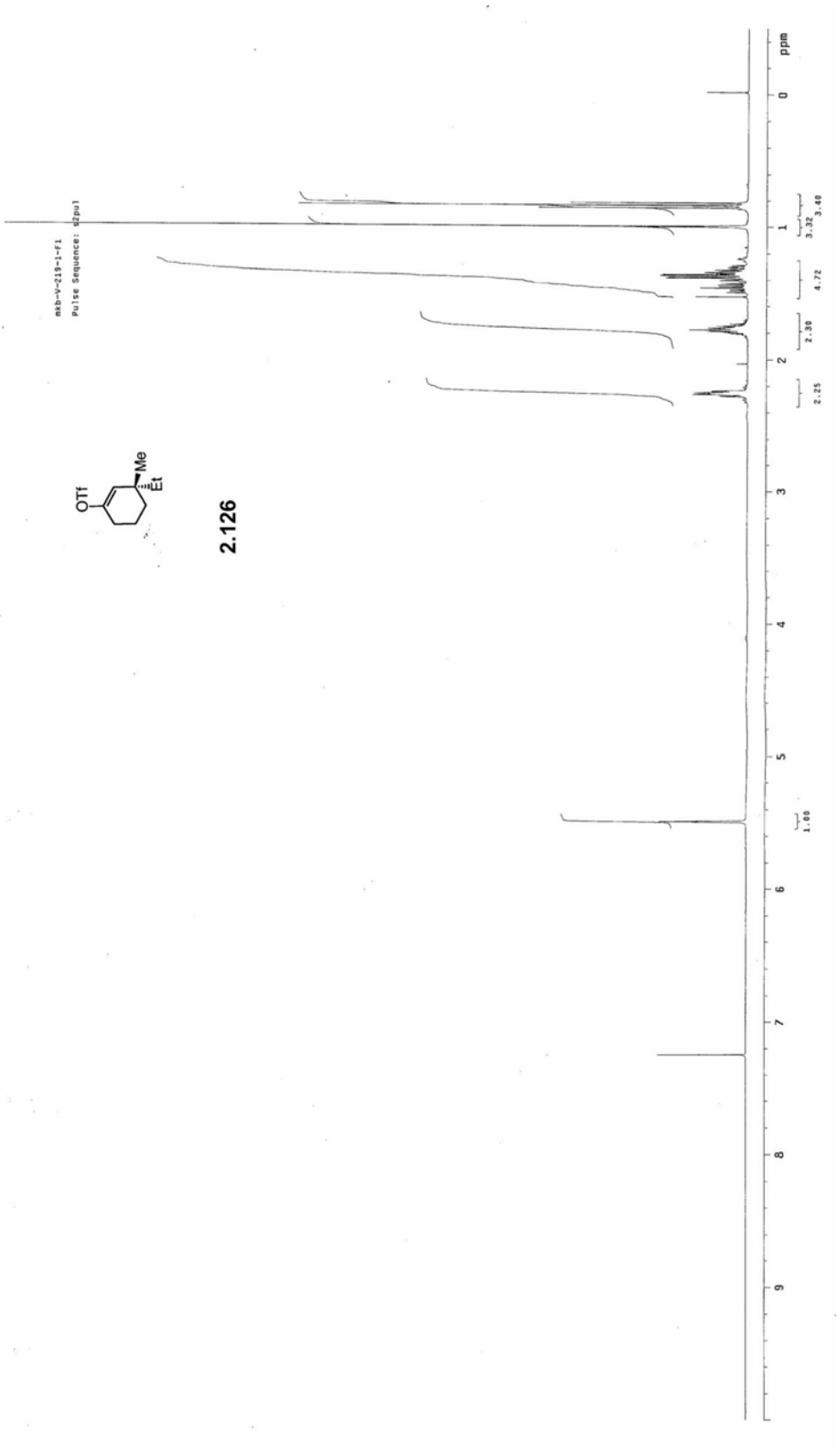
Me
ppm



2.124



2.125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Et
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7
8
9
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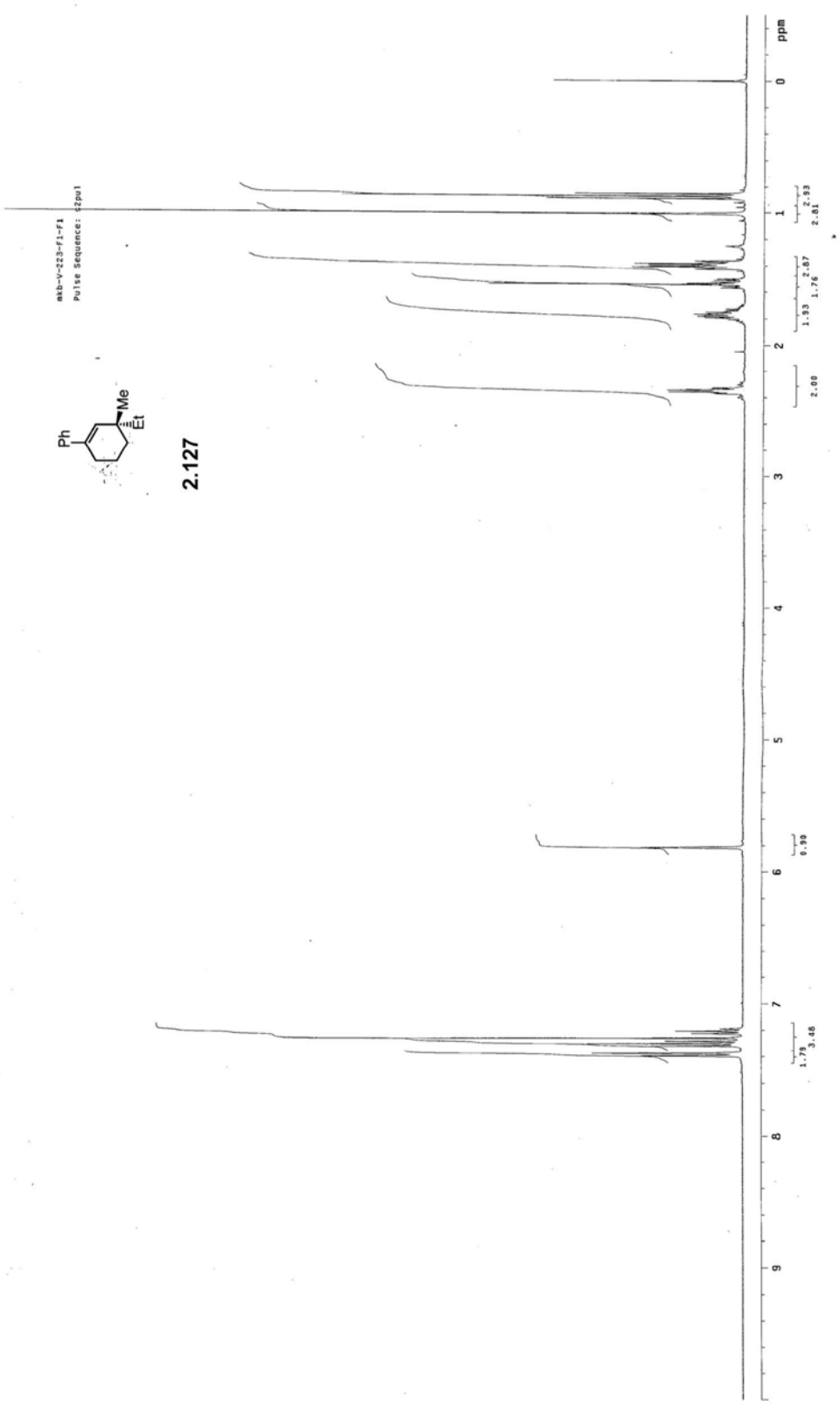
2.25
2.30
4.72
3.32
3.40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Ph
Me
Et
2.127
ppm
0
1
2
3
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6
7
8
9
2.93
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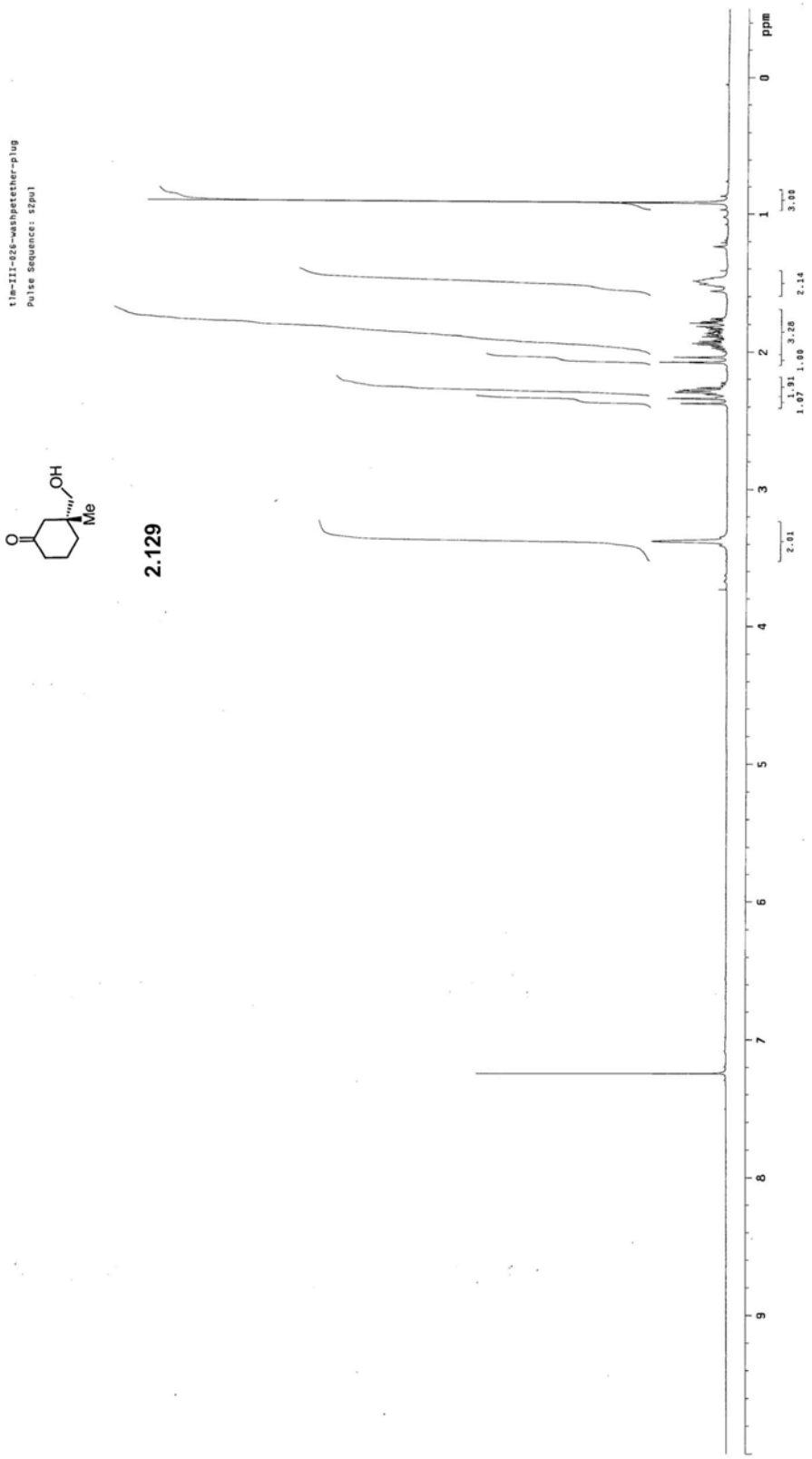
2.87
1.76
1.93
2.00
6.99
1.79
3.48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OH
Me
O
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ppm
0
1
2
3
4
5
6
7
8
9
3.00
2.14
3.28
1.91
1.07
1.00
2.01

Chapter 3. Enantioselective Total Synthesis of Clavirolide C: A Platform for New Methods and Catalyst Development

3.1 *Introduction*

One of the primary objectives in complex molecule total synthesis is to identify and provide solutions to difficult problems in chemical synthesis. In the context of addressing these problems, we are forced to test the limits of established catalysts in new and difficult settings, as well as develop new catalysts to carry out transformations once thought unattainable. Herein, we present an efficient enantioselective total synthesis of (–)-clavirolide C (**3.1**)[126] (Figure 3.1) where we address important methods for carbon-carbon bond formation. These studies have forced us to (1) develop a new catalyst system for ACA of trialkylaluminium reagents to β-substituted cyclopentenones, (2) test the limits of Ru-based olefin metathesis catalysts olefin and (3) identify a problem for stereoselective aldol additions that awaits further development.

3.2 *Background*

The clavirolides are members of the dolabellane family of diterpenes, isolated from Pacific soft coral *Clavularia viridis*, and contain a characteristic *trans*-

(126) "Four Novel Diterpenoids: Clavirolide B, C, D, and E From the Chinese Soft Coral *Clavularia Viridis*," Su, J.; Zhong, Y.; Zeng, L. *J. Nat. Prod.* **1991**, *54*, 380-385.

bicyclo[9.3.0]tetradecane core (Figure 3.1).[126,127] The all-carbon quaternary stereogenic center at the junction of the medium ring and cyclopentane moiety presents a unique challenge to the synthetic chemist. While no completed total syntheses of any of the clavirolides have been reported, several groups have published synthesizes of various segments of these molecules.[128]

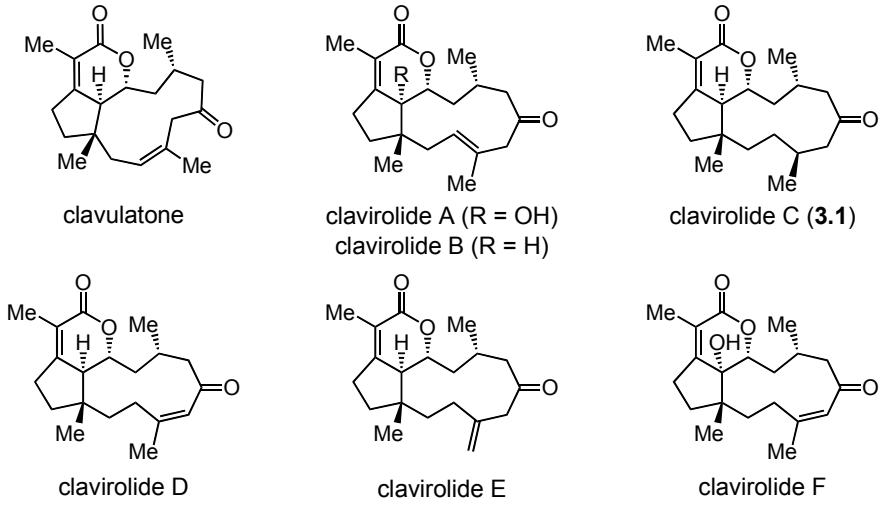


Figure 3.1: Clavulactone and the Clavirolides

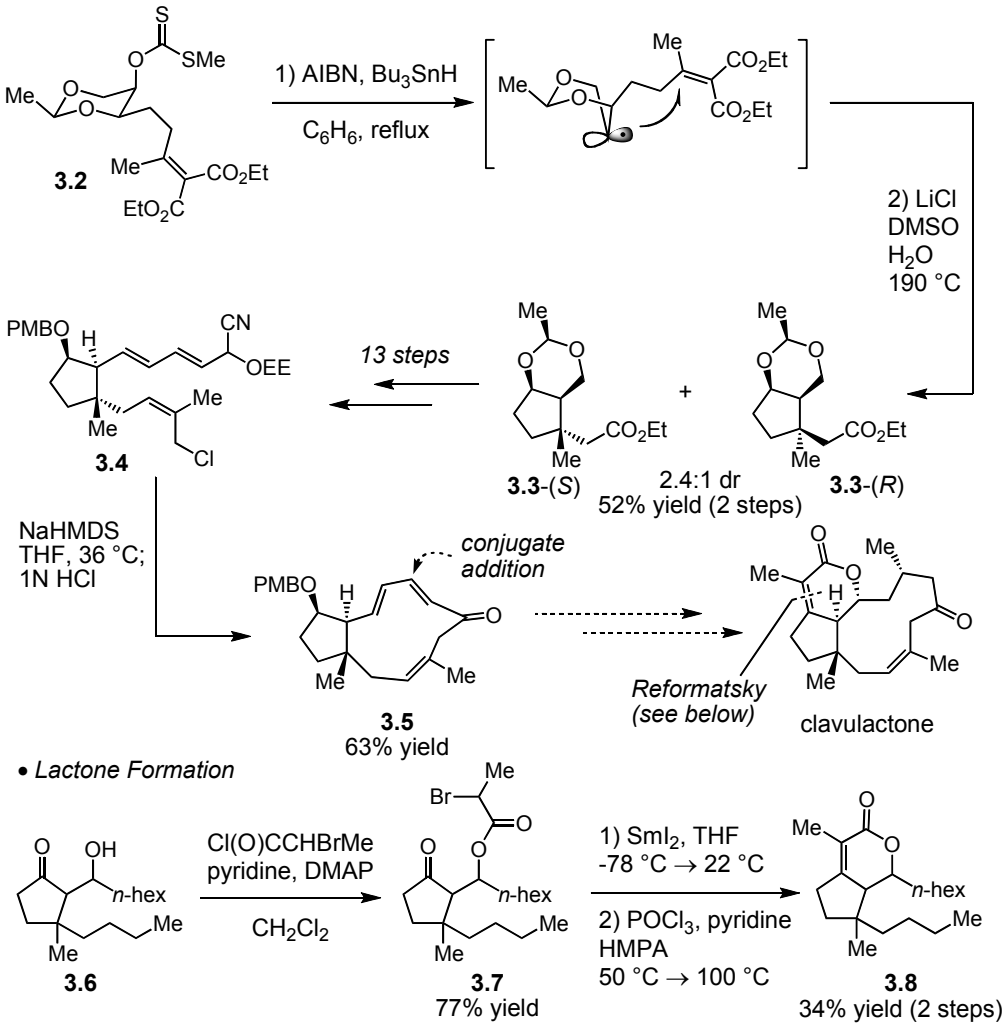
In 2001, Wu and coworkers disclosed preliminary studies toward total synthesis of clavulactone by establishing a viable route to dienone **3.5** (Scheme 3.1).[128a] Central to their strategy was a stereospecific rearrangement of xanthate **3.2** to establish the difficult to prepare all-carbon quaternary stereogenic center (**3.2** → **3.3**, 2.4:1 dr, 53% yield, 2

(127) For reviews on Dolabellane natural products, see: "The Structural Chemistry, Reactivity, and Total Sythesis of Dolabellane Diterpenes," Rodrígues, A. D.; González, E.; Ramírez, C. *Tetrahedron*, **1998**, *54*, 11683-11729.

(128) (a) "Studies Toward the Total Synthesis of Clavulactone," Zhum, Q.; Qiao, L.; Wu, Y., Wu, T-L. *J. Org. Chem.* **2001**, *66*, 2692-2699. (b) "Model Studies for the Synthesis of Clavulactone," Zeng, Z.; Xu, X. *Tetrahedron Lett.* **2000**, *41*, 3459-3461. (c) "General Synthetic Approach to Bicyclo[9.3.0]tetradecenone," A Versatile Intermediate to Clavulactone and Clavirolides" Sun, B.; Xu, X. *Tetrahedron Lett.* **2005**, *46*, 8431-8434. (d) "Stereospecific Rearrangement of α-Hydroxyepoxide: Efficient Approach to the *trans*-Bicyclo[9.3.0]tetradecane Core En Route to Clavulactone," Sun, B.; Xu, X. *Tetrahedron Lett.* **2006**, *47*, 299-302.

steps). Synthetic manipulations of cyclopentane **3.3** provided **3.4** in 13 steps. Cyclization to prepare 11-membered ring **3.5** proceeded readily in 63% yield. Wu and coworkers envisioned that after several transformations of **3.5**, including conjugate addition to the dienone moiety, the unsaturated lactone unit could be installed through a Reformatsky/dehydration sequence. Model studies have already been carried out to demonstrate the validity of this process. Esterification of alcohol **3.6** provided **3.7** in 77% yield. Samarium diiodide mediated Reformatsky addition, followed by dehydration with $POCl_3$ in HMPA, furnished **3.8** in 34% yield over 2 steps.

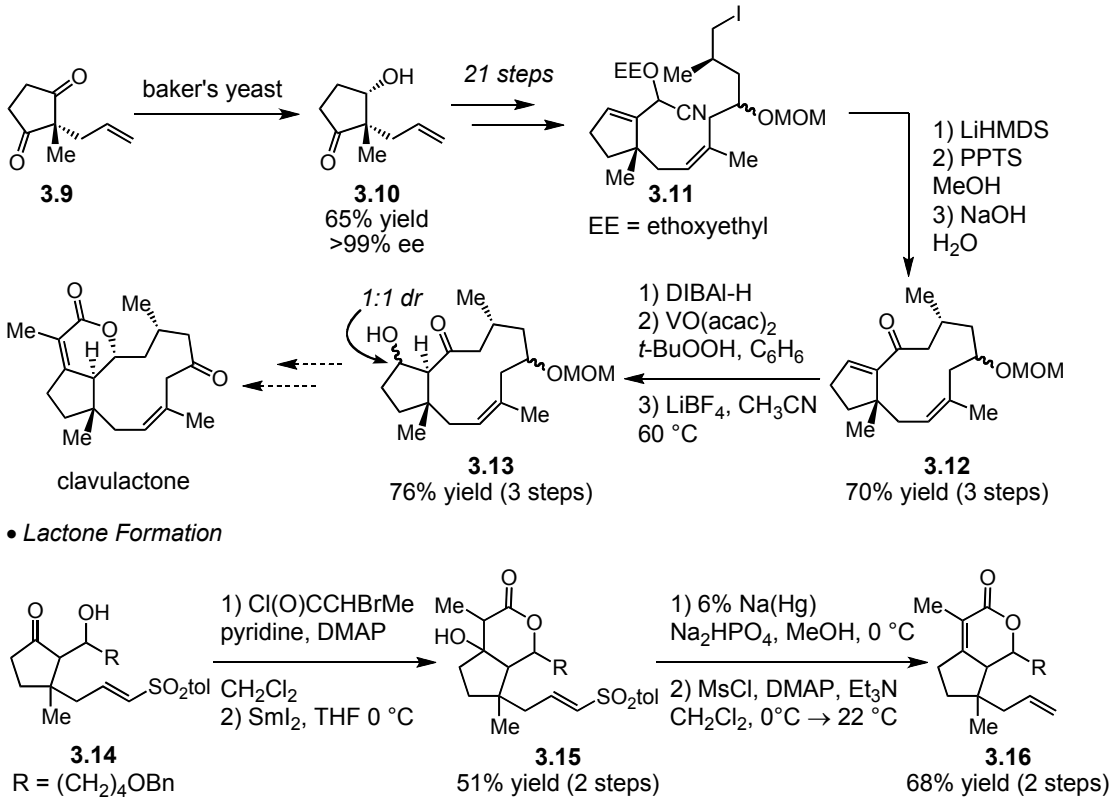
Scheme 3.1: Studies Toward Total Synthesis of Clavulactone by Wu



Xu and coworkers have prepared **3.13** en route to a potential intermediate toward the synthesis clavulactone (Scheme 3.2).[128c-d] The all-carbon quaternary stereogenic center was established by a microbial reduction of diketone **3.9**, mediated by baker's yeast to deliver **3.10** in >99% ee and 65% yield. Chemical transformations of **3.10** provided **3.11** in 21 steps, which was poised to undergo 11-membered ring formation. Treatment of **3.11** with LiHMDS followed by hydrolysis and dehydration furnished enone **3.12** in 70% yield over 3 steps. Reduction of the ketone with dibal-H, followed by

Sharpless directed epoxidation, afforded the corresponding epoxy alcohol (not shown). Stereospecific 1,2-hydride migration, mediated by $LiBF_4$, delivered β-hydroxy ketone **3.13** in 76% yield over 3 steps (1:1 dr). Advancement of either diastereomer of **3.13** to clavulactone was unsuccessful. Similar to studies carried out by Wu, Xu has demonstrated that the unsaturated lactone moiety could be established through a Reformatsky/dehydration sequence (**3.14** → **3.16**).[128b]

Scheme 3.2: Studies Toward Total Synthesis of Clavulactone: Xu and Coworkers



3.3 *Enantioselective Total Synthesis of Clavirolide C*

3.3.a Retrosynthesis

The retrosynthesis of clavirolide C is illustrated in Figure 3.2. We envisioned that the angular methyl group at C4 could be established through a conjugate addition to intermediate **3.I**. The 11-membered ring could be installed though a catalytic ring-closing metathesis (RCM) of diene **3.II**, itself readily available from intermediate **3.III**. Diene **3.III** may be prepared through an aldol addition between aldehyde **3.IV** and enolate **3.V**. Intermediates **3.IV** and **3.V** could be prepared through Cu-catalyzed asymmetric conjugate addition (ACA) reactions. This retrosynthesis highlights several unsolved problems in chemical synthesis: (1) Catalytic ACA to cyclopentenone derivatives to afford all-carbon quaternary stereogenic centers (preparation of intermediate **3.V**). (2) Stereoselective aldol addition between cyclopentanone-derived enolates and aliphatic aldehydes (**3.V**+**3.IV**→**3.III**).

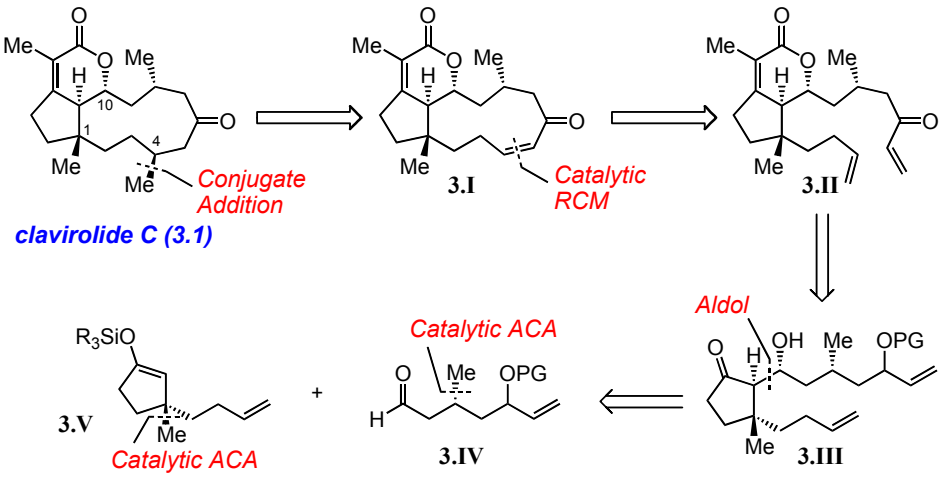


Figure 3.2: Retrosynthesis of Clavirolide C

3.3.b Cu-Catalyzed Asymmetric Conjugate Additions (ACAs) to Unactivated β-Substituted Cyclopentenones

3.3.b.1 Background

While several methods have been reported for highly enantioselective Cu-catalyzed ACA of alkylmetals to afford all-carbon quaternary stereogenic centers,[129,130] most do not address additions to the more difficult *β*-substituted cyclopentenones.[131] This section will briefly outline the state-of-the-art for ACA of organometals to β-alkyl-substituted cyclopentenones.

In the first reported example for Cu-catalyzed ACA to β-substituted cyclopentenones additional activation of the enone was required to achieve efficient and

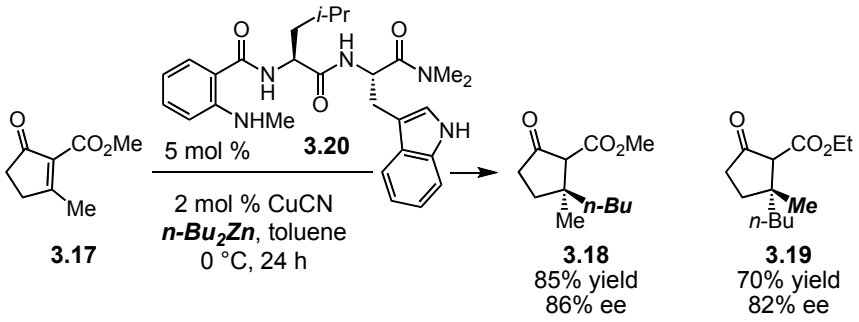
(129) (a) "Recent Advances in Catalytic Enantioselective Michael Additions," Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171-196. (b) "Enantioselective Copper-Catalyzed Conjugate Addition," Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221-3236. (c) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. in *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, pp. 224-258. (d) "Recent Advances in Metal-Catalyzed Asymmetric Conjugate Additions," Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279-1300. (e) "Formation of All-Carbon Quaternary Centers by Copper-Catalyzed Asymmetric Conjugate Addition," Alexakis, A.; Vuagnoux-d'Augustin, M.; Martin, M.; Kehrli, S.; Palais, L.; Henon, H.; Hawner, C. *Chima* **2008**, *62*, 461-464. (f) "Enantioselective Copper-Catalyzed Conjugate Addition and Allylic Substitution Reactions," Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796-2823.

(130) (a) "Stereoselective Formation of Quaternary Carbon Centers and Related Functions," Denissova, I.; Barriauit, L. *Tetrahedron*, **2003**, *59*, 10105-10146. (b) "Asymmetric Catalysis Special Feature Part I: Catalytic Asymmetric Synthesis of All-Carbon Quaternary Stereocenters," Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363-5367. (c) Christophers, J.; Baro, A. (Eds.), *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis,* Wiley-VCH, Weinheim, **2006**.

(131) Cu-catalyzed ACA to cyclopentenone derived substrates are more challenging. For examples, see: (a) "New Chiral Oxazoline-Phosphite Ligands for the Enantioselective Copper-Catalyzed 1,4, Addition of Organozinc Reagents to Enones," Escher, I. H.; Pfaltz, A. *Tetrahedron* **2000**, *56*, 2879-2888. (b) "Modular Peptide-Based Phosphine Ligands in Asymmetric Catalysis: Efficient and Enantioselective Cu-Catalyzed Conjugate Additions to Five-, Six- and Seven-Membered Cyclic Enones," Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755-756. (c) "Enantioselective 1,4-Addition of Diorganozinc Reagents to Cyclic Enones Using Chiral Diphosphite Ligands Derived from H_8-Binaphthol," Liand, L.; Au-Yeung, T. T-L.; Chand, A. S. C. *Org. Lett.* **2002**, *4*, 3799-3801.

selective additions with dialkylzinc reagents (Scheme 3.3).[132] While this method might be suitable, preparation of enol silane intermediate **3.V** would likely require several transformations from **3.18** or **3.19**.

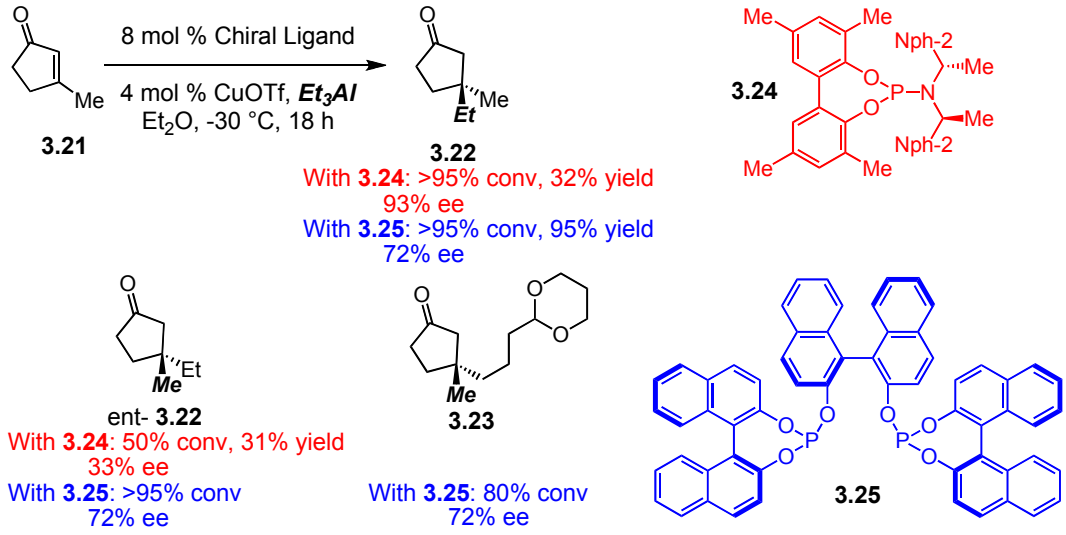
Scheme 3.3: Enantioselective Conjugate Addition to Activated Enones by Hoveyda



As illustrated in Scheme 3.4, enantioselective additions involving unactivated *β*-substituted cyclopentenones have been shown to afford products with either high enantioselectivity (95% ee, 32% yield for **3.22**, reaction with **3.24**)[133] or in high yield (72% ee, 95% yield for **3.22**, catalyzed by **3.25**);[134] however at the time we initiated our studies, there were no methods that provide the desired products with both high efficiency and enantioselectivity. Furthermore, conversions begin to suffer when the size of the β-substituent is increased (synthesis of **3.23**, 80% conv, 72% ee).

(132) "Catalytic Enantioselective Alkylations of Tetrasubstituted Olefins. Synthesis of All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Enones," Hird. A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988-14989.
(133) "Enantioselective Copper-Catalyzed Conjugate Addition to 2- or 3-Substituted Cyclopent-2-en-1-ones: Construction of Stereogenic Quaternary Carbon Centers," Vangnoux-d'Augustin, M.; Kehrli, S.; Alexakis, A. *Synlett*, **2007**, *13*, 2057-2060.
(134) "Copper-Catalyzed Asymmetric Conjugate Addition of Trialkylaluminium Reagents to Trisubstituted Enones: Construction of Chiral Quaternary Centers," Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem. Eur. J.* **2007**, *13*, 9647-9662.

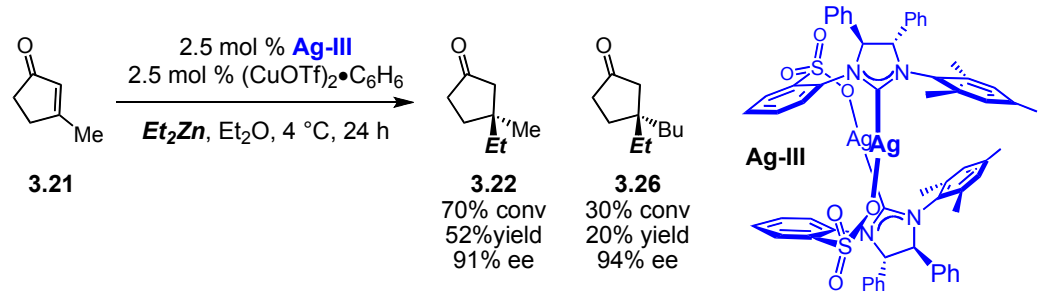
Scheme 3.4: Enantioselective Conjugate Addition to Unactivated Enones by Alexakis



We have been able to carry out highly enantioselective (91-94% ee) additions to β-substituted cyclopentenones with chiral NHC-based ligand **Ag-III** (Scheme 3.5);[135,136,137] however, efficiency was an issue, especially with enones bearing slightly larger susbtituents (Bu vs. Me), as judged by the formation of **3.26** (30% conv). It is important to note that additions of Me_2Zn under a variety of conditions led to <2% conv.

(135) For the initial report regarding synthesis and use of **Ag-III**, see: "All-Carbon Quaternary Stereogenic Centers by Enantioselective Cu-Catalyzed Conjugate Additions Promoted by a Chiral N-Heterocyclic Carbene," Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097-1100.
(136) For a full discussion of this method and related ACAs promoted by chiral NHC complexes, see: Chapter 2.
(137) These studies were carried out with Mikiko Akiyama.

Scheme 3.5: Enantioselective Conjugate Additions to Unactivated Enones by Hoveyda



3.3.b.2 Optimization of ACA of $AlMe_3$ to β-Substituted Cyclopentenones

Initial results were encouraging for enantioselective synthesis of the requisite all-carbon quaternary stereogenic center, necessary for total synthesis of clavirolide C. The previously identified optimal conditions[136] for additions of *diethylzinc* to β-substituted cyclic enones (Scheme 3.5) proved ineffective (<2% conv) for alkylation with the typically less reactive *dimethylzinc*. We therefore turned our attention to the more Lewis acidic Me_3Al reagent and observed a substantial increase in reactivity (Table 3.1).[138,139] Model substrate **3.27** underwent alkylation with Me_3Al in a highly efficient manner (92->98% conv, 15 h) with moderate selectivity (16-47% ee) when promoted by chiral NHCs **Ag-I**,[140] **Ag-II**[141] and **Ag-III**[135] (Table 3.1, entries 1-3). Since **Ag-III** provided **3.28** with

(138) For a review regarding the use of aluminum based nucleophiles, see: "Selectivity Control in 1,2- and 1,4-Additions of Aluminum Organyls to Carbonyl Compounds," von Zezechwita, P. *Synthesis*, **2008**, 1809-1831.
(139) For enantioselective Cu-catalyzed conjugate additions with triorganoaluminum reagents to afford all-carbon quaternary stereogenic centers, see: (a) "Enantioselective Copper-Catalyzed Conjugate Addition to Trisubstituted Cyclohexenones: Construction of Stereogenic Quaternary Centers," d'Augustin, M.; Palais, L.; Alexakis, A. *A. Angew. Chem., Int. Ed.* **2005**, *44*, 1376-1378. (b) ref (134). (c) ref (133).
(140) "Bidentate NHC-Based Chiral Ligands for Efficient Cu-Catalyzed Enantioselective Allylic Alkylations: Structure and Activity of an Air-Stable Chiral Cu Complex," Larsen, A. O.; Leu, J.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130-11131.
(141) "A Readily Available Chiral Ag-Based N-Heterocyclic Carbene Complex for Use in Efficient and Highly Enantioselective Ru-Catalyzed Olefin Metathesis and Cu-Catalyzed Allylic Alkylation Reactions,"

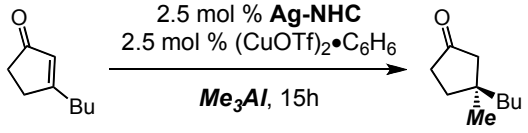
the highest enantioselectivity, we chose to optimize the reaction further with this chiral ligand.[142] With reactions carried out in Et_2O, a slight increase in enantioselectivity was observed at lower temperature (-55 °C), however, conversion suffered (Table 3.1, compare entries 4 and 5). Screening various solvents led to the discovery that reactions in THF at –30 °C gave rise to identical selectivity as Et_2O (Table 3.1, entry 9). Furthermore, when THF is employed, a decrease in temperature (-78 °C vs. -30 °C), leads to higher enantioselectivity without a loss in efficiency (Table 3.1, compare entries 9 and 10). It is important to note that 15 Cu-salts were examined and all afford the product in moderate to excellent conversion (62->98%) but with identical selectivity (50% ee).[143]

Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877-6882.

(142) Background reactions: <2% conversion was observed at –30 °C in Et_2O or THF under the following sets of conditions: $(CuOTf)_2 \bullet C_6H_6$; Imidazolinium salt (precursor to **Ag-III**) and $(CuOTf)_2 \bullet C_6H_6$; or complex **Ag-III**.

(143) Select examples: Cu-catalyzed ACA of Me_3Al promoted by 5 mol % **Ag-III**, 5 mol % Cu salt, THF, -30 ^oC, 15 h: $CuCl_2 \bullet 2H_2O$, 92% conv, 50% ee; CuCN, 62% conv, 50% ee; CuI, 95% conv, 50% ee; $Cu(OTf)_2$, 99% conv, 50% ee; CuTC, 88% conv, 50% ee; $(MeCN)_4CuPF_6$, 96% conv, 50% ee.

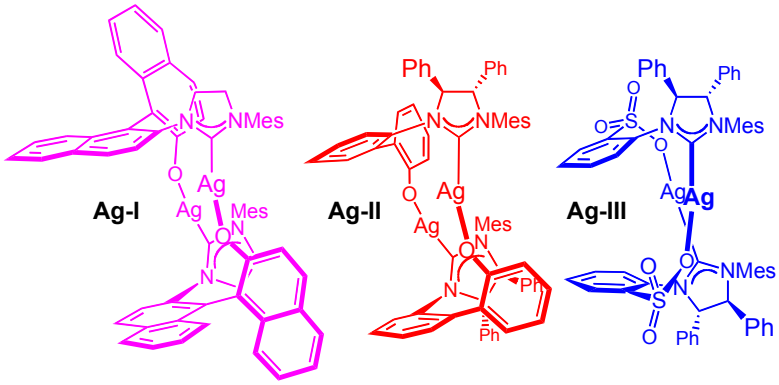
Table 3.1: Initial Screening of Various Conditions For Cu-Catalyzed ACA



3.27 **3.28**

entry	Ag-NHC	solvent	temp (°C)	conv (%)[a]	ee (%)[a]
1	**Ag-I**	Et_2O	-15	92	16
2	**Ag-II**	Et_2O	-15	>98	35
3	**Ag-III**	Et_2O	-15	>98	47
4	**Ag-III**	Et_2O	-30	>98	50
5	**Ag-III**	Et_2O	-55	70	60
6	**Ag-III**	*t*-BuOMe	-30	79	17
7	**Ag-III**	DME	-30	>98	51
8	**Ag-III**	toluene	-30	85[b]	--
9	**Ag-III**	THF	-30	>98	50
10	***Ag-III***	***THF***	***-78***	***95***	***60***

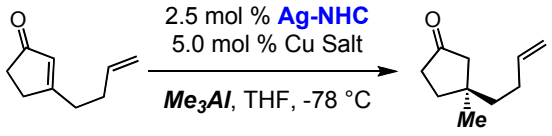
[a] Determined by chiral GLC. [b] Complex mixture



At this point in our studies, we decided to examine β-butenyl substituted cyclopentenone **3.29** and, unexpectedly, this substrate proved to be *less reactive* (48% conv, 15 h, -78 °C) and less selective (49% vs. 60% ee) than saturated analog **3.27** (Table 3.2, entry 1). The lower reactivity associated with **3.29** may be due to coordination of the terminal alkene with the catalytically active Cu(I) complex, which may lead to a less active species. Examination of various Ag-NHC complexes led to the discovery that the use of modified **Ag-IV** led to a marked improvement in enantioselectivity (71% ee, Table

3.2, entry 2) as well as a slight improvement in conversion (69%). We synthesized **Ag-IV**, which lacks an aryl group on the diamine backbone, with the hypothesis that steric presence of the mesityl unit would be enhanced by allowing free rotation about the C-N bond.[144] Conversion was further improved to 97% by use of $Cu(OTf)_2$ (vs. $(CuOTf)_2 \bullet C_6H_6$) along with extension of the reaction time to 36 h (vs. 15 h; Table 3.2, entry 4).[145] We were able to increase the enantioselectivity by employing 2,6-diethylaryl (vs. mesityl) **Ag-V**, which provided **3.30** in 86% ee and 80% yield (Table 3.2, entry 3). Under these optimized conditions (THF, $Cu(OTf)_2$, -78 °C, 36 h), use of **Ag-III** provided **3.30** in 49% ee (75% conv) (Table 3.2, entry 6).

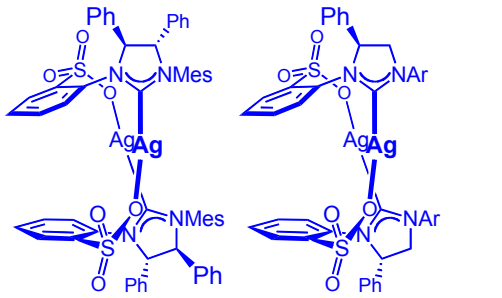
Table 3.2: Final Optimization of Reaction Conditions and Chiral NHC



3.29 **3.30**

entry	Ag-NHC	Cu salt	time (h)	conv (%)[a]	ee (%)[a]
1	**Ag-III**	CuOTf[b]	15	48	49
2	**Ag-IV**	CuOTf[b]	15	69	71
3	**Ag-IV**	$Cu(OTf)_2$	15	80	72
4	**Ag-IV**	$Cu(OTf)_2$	36	97	72
5	***Ag-V***	***$Cu(OTf)_2$***	***36***	***86***	***86***
6	**Ag-III**	$Cu(OTf)_2$	36	74	49

[a] Determined by chiral GLC.
[b] 2.5 mol % $(CuOTf)_2 \bullet C_6H_6$



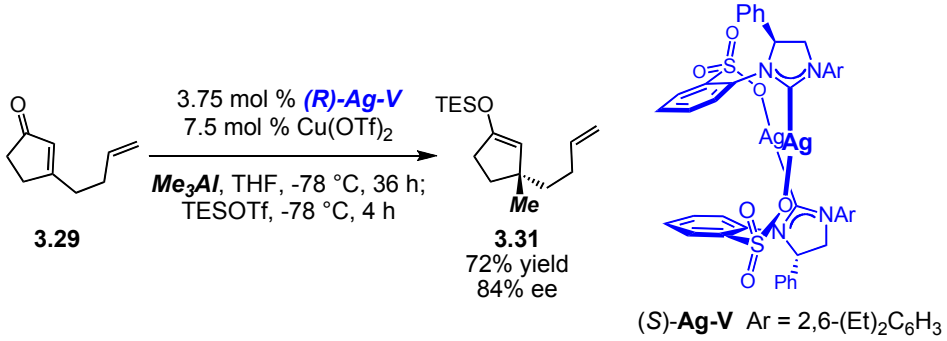
Ag-III **Ag-IV** Ar = Mes
Ag-V Ar = 2,6-$(Et)_2C_6H_3$

For purposes of the synthesis, the Al-enolate was trapped as the corresponding silylether with TESOTf to deliver **3.31** in 72% yield and 84% ee (Scheme 3.6). Slightly

(144) For a previous disclosure of this complex and its application to Cu-catalyzed AAA, see: "Highly Site- and Enantioselective Cu-Catalyzed Allylic Alkylation Reactions with Easily Accessible Vinylaluminum Reagents" Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*. 446-447.
(145) For unknown reasons, reactions tended to be more reproducible with Cu(II) rather than Cu(I) salts.

higher catalyst loading (7.5 mol % vs. 5 mol %) was employed to ensure that the reaction proceeded to completion prior to trapping as the TES ether. This was done to avoid nonselective conjugate addition, which could occur upon introduction of the highly Lewis acidic TESOTf to the reaction mixture.

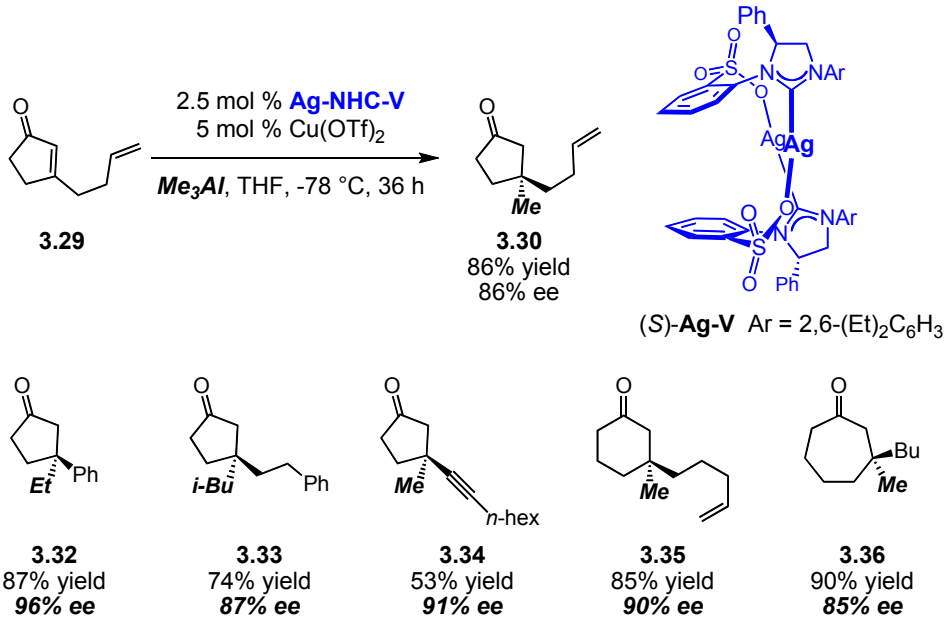
Scheme 3.6: Synthesis of Enol Silane **3.31**



As illustrated in Scheme 3.7, additions of a variety of trialkylaluminum reagents, including the sterically-hindered *i*-Bu_3Al to five-, six-, and seven-membered ring enones have been carried out.[146] Enantioselectivities were generally higher in reactions involving cyclopentenones when compared to reactions of larger ring sizes (compare **3.30**-**3.34** and **3.35**-**3.36**). Even substrates that bear a sterically bulky β-Ph (formation of **3.32**) or sterically small β-alkynyl (formation of **3.34**) substituent are tolerated and these products are obtained in high ee (91-96% ee).

(146) These studies were carried out by Tricia L. May. "Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers by Catalytic Asymmetric Conjugate Additions of Alkyl- and Arylaluminum Reagents to Five-, Six- and Seven-Membered Ring β-Substituted Cyclic Enones," May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358-7362.

Scheme 3.7: Cu-Catalyzed ACA of Trialkylaluminium Reagents

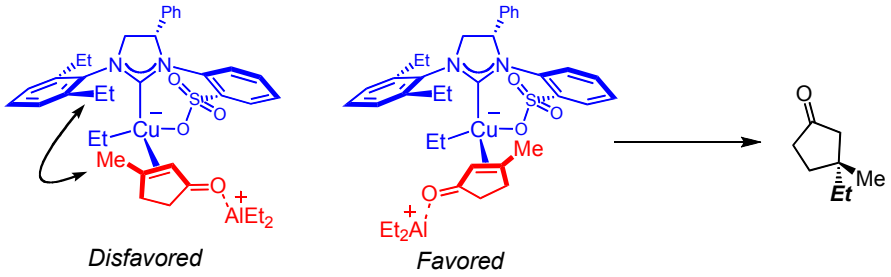


We have proposed a working transition state model that accounts for the increased selectivity observed with reactions involving **Ag-IV** or **Ag-V** vs. **Ag-III** (Scheme 3.8). Omission of one of the phenyl groups of the diamine backbone may allow the proximal aryl unit to rotate more freely. Thus, the effective size of the aryl ring may be enlarged, which, in the disfavored complex, would increase the steric interaction between the β-substituent of the enone substrate and the aryl unit of the catalyst (Scheme 3.8). In contrast to mechanistic models proposed for related reactions involving dialkylzinc reagents,[147] where bidentate coordination of the enone substrate is suggested, we propose monodentate complexation of the enone in this case. Due to the increased Lewis acidic nature of Al(III) species (vs. Zn(II)), the enone may be sufficiently activated and thus

(147) For discussion, see: Chapter 2, section 2.4.b.6

would not require bidentate coordination. Therefore, we propose the enone binds in such a manner that steric interactions with the 2,6-diethylaryl unit are minimized.

Scheme 3.8: Working Mechanistic Models



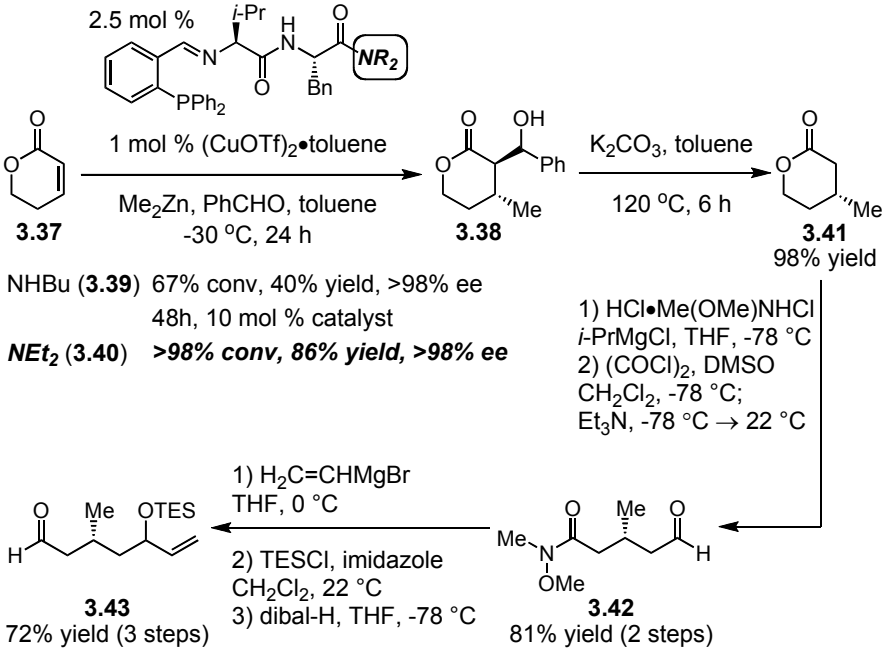
3.3.c Synthesis of Chiral Aldehyde 3.43

Synthesis of aldehyde **3.43** commenced with Cu-catalyzed ACA to unsaturated lactone **3.37** (Scheme 3.9).[148] Chiral ligand **3.39** that was developed for ACA to unsaturated lactones was not efficient for addition of Me_2Zn to six-membered ring substrate **3.37**, as the desired product **3.38** was delivered in 40% yield (67% conv, 48 h, 10 mol % catalyst) and >98% ee. We were able to optimize this transformation by employing ligand **3.40**, bearing an NEt_2 terminus, and **3.38** was obtained in 86% yield (>98% conv, 24 h, 2.5 mol %) and >98% ee.[149] Retroaldol reaction promoted by K_2CO_3 delivered lactone **3.41** in 98% yield. Opening of lactone **3.41** with Weinreb amine, followed by oxidation of the generated primary alcohol provided aldehyde **3.42** in 81%

(148) For discussions regarding this method, see: (a) Chapter 1. (b) "Highly Enantioselective Cu-Catalyzed Conjugate Additions of Dialkylzinc Reagents to Unsaturated Furanones and Pyranones: Preparation of Air-Stable and Catalytically Active Cu-Peptide Complexes," Brown, M. K.; Degrado, S. J. Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306-5310.
(149) This modification was employed in related Cu-catalyzed ACA to nitroalkenes. "Efficient Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Aromatic and Aliphatic Acyclic Nitroalkenes," Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2002**, *6*, 2829-2832.

yield over 2 steps.[150] Addition of vinylmagnesium bromide, followed by silyl protection and reduction with dibal-H, furnished **3.43** (72% yield, 3 steps).[151]

Scheme 3.9: Synthesis of Chiral Aldehyde **3.43**

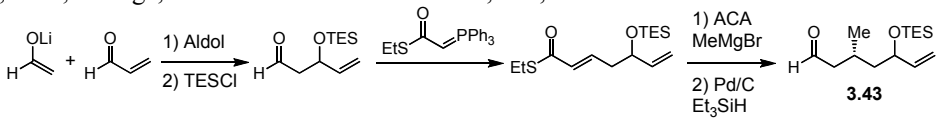


3.3.d Aldol Addition

In order to test the feasibility of the proposed aldol addition of enol silane **3.31** to aldehyde **3.43**, we carried out the model studies outlined in Table 3.3. Mukaiyama aldol

(150) Weinreb amide was prepared following a literature procedure; see: "A New General Method for Preparation of *N*-Methoxy-*N*-Methylamides. Application in Direct Conversion of an Ester to a Ketone," Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461-5464.

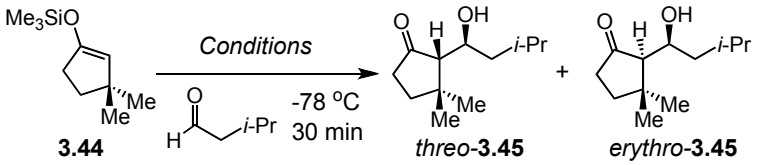
(151) A potential alternative synthesis of **3.43**, featuring Cu-catalyzed ACA of MeMgBr to unsaturated thio-ester is illustrated below. For a reference regarding the ACA methodology, see: "An Iterative Catalytic Route to Enantiopure Deoxypropionate Subunits: Asymmetric Conjugate Addition of Grignard Reagents to α,β-Unsaturated Thioester," Des Mazery, R.; Pullez, M.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 9966-9967.



addition of enol silane **3.44** to isovaleroaldehyde, promoted by $TiCl_4$, led to preferential formation of the *erythro*-diastereomers **3.45**, likely because the reaction proceeded though an open transition state (Table 3.3, entry 1).[152] In order to reverse the selectivity to generate the desired *threo*-diastereomers, we decided to examine conditions that favor a closed transition state. We were able to establish that generation of a lithium enolate in Et_2O followed by treatment with isovaleroaldehyde, delivered the desired *threo*-diastereomer **3.45** as the major product (72:28 *threo*:*erythro*) in 75% yield (Table 3.3, entry 2).[153] Due to the coordinating nature of THF, aldol additions in this solvent were non-selective (Table 3.3, entry 3). Reactions carried out in less coordinating solvents (*t*-BuOMe, pentane, toluene) than Et_2O failed to convert enol silane **3.44** to the lithium enolate (Table 3.3, entries 4-6). Conversion of the lithium enolate to either Zn, Sn or Ti enolates and addition of isovaleroaldehdye provided **3.45** generally favoring the *erythro*-diastereomer **3.45** (Table 3.3, entries 8-10).

(152) "New Cross-Aldol Reactions. Reactions of Silyl Enol Ethers with Carbonyl Compounds Activated by Titanium Tetrachloride," Mukaiyama. T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 6061-6101.
(153) "Acyclic Stereoselection. 7. Stereoselective Synthesis of 2-Alkyl-3-hydroxy Carbonyl Compounds by Aldol Condensation," Heathcock, C. H.; Buse, C. T.; Kleschinck, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081.

Table 3.3: Model Studies for Aldol Addition



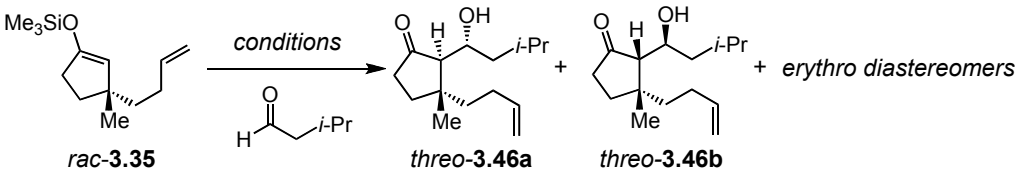
entry	conditions	yield (%)[a]	*threo:erythro*[b]
1	$TiCl_4$, CH_2Cl_2	66	25:64
2	***n-BuLi, Et_2O***	***75***	***72:28***
3	n-BuLi, THF	54	50:50
4	*n*-BuLi, *t*-BuOMe	<15	50:50
5	*n*-BuLi, pentane	<2	--
6	*n*-BuLi, toluene	<2	--
7	*n*-BuLi, Et_2O; TMEDA	nd	67:33
8	*n*-BuLi, Et_2O; $ZnCl_2$	nd	25:75
9	*n*-BuLi, Et_2O; $ClSnBu_3$	nd	50:50
10	*n*-BuLi, Et_2O; $Ti(Oi\text{-}Pr)_4$	nd	20:80

[a] Yield of isolated product. [b] Determined by ^1H NMR analysis of the unpurified reaction mixtures.

Further optimization was carried out with enol silane *rac*-**3.35** (Scheme 3.10). These studies revealed that generation of the lithium enolate in THF, followed by treatment with 3 equiv BEt_3 and isovaleroaldehyde, delivered **3.46a** as the major product (88:12 *threo*:*erythro*, 4:1 **3.46a**:**3.46b**).[154] It is likely that the reason for increased diastereoselectivity with BEt_3 stems from the fact that a boron enolate is generated in situ; it is well established that aldol reactions with boron enolates proceed through highly ordered, closed transition states (Scheme 3.10).[155] The rational for increase selectivity requires excess BEt_3 to generate the dialkylboron enolate. Therefore, as expected aldol addition carried out with 1.0 equiv BEt_3 led to a non-selective reaction (50:50, *threo:erythro*, Scheme 3.10).

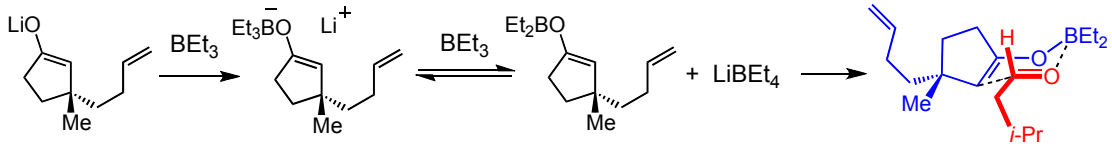
(154) "*Threo*-Selective Aldol Condensations of Lithium Enolate in the Presence of Trialkylboranes," Yamamoto, Y.; Yatagai, H.; Maruyama, K. *Tetrahedron Lett.* **1982**, *23*, 2387-2390.
(155) "Stereoselective Aldol Condensations via Boron Enolates," Evans, D. A.; Nelson, J. V.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099-3111.

Scheme 3.10: Model Studies for Aldol Addition



n-BuLi, Et_2O, -78 °C	50	:	25	:	25
***n*-BuLi, THF; 3.0 equiv BEt_3, -78°C**	***70***	:	***18***	:	***12***
n-BuLi, THF; 1.0 equiv BEt_3, -78°C	25	:	25	:	50

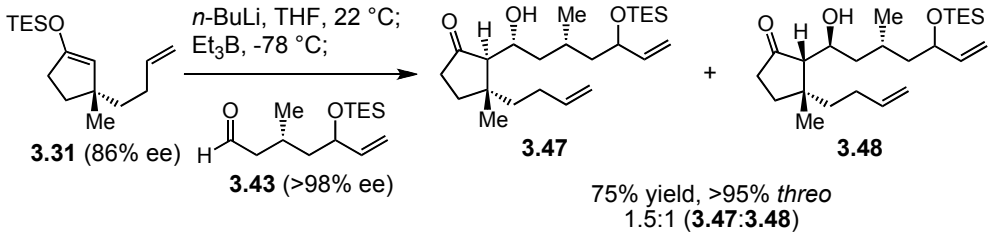
• *Rational for Increased Selectivity with BEt_3*



While this aldol addition is far from fully optimized, we decided that the current level of diastereoselectivity was sufficient to continue with the synthesis. Thus, aldol addition between enol silane **3.31** and aldehyde **3.43** provided *β*-hydroxy ketone **3.47** (and the corresponding diastereomer **3.48**, derived from aldehyde approach syn to the butenyl group) in 75% combined yield (1.5:1 **3.47**:**3.48**, Scheme 3.11). Diastereoselectivity increased compared to the model system with respect to the threo:erythro diastereomeric ratio (88% vs. >95% *threo*); however, facial selectivity decreased (aldehyde approach syn-to-methyl vs. syn-to-butenyl. 4:1 vs. 1.5:1) when compared to the model system (Scheme 3.10). The low diastereoselectivity observed is likely due to the small steric difference between the methyl and butenyl groups. Ideally, the stereoselectivity could be controlled by use of a chiral catalyst/reagent, however no

enantioselective methods have been reported to carry out aldol addition of *cyclopentanone*-derived enolates to *aliphatic* aldehydes.

Scheme 3.11: Aldol Addition of Enol Silane **3.31** to Aldehyde **3.43**



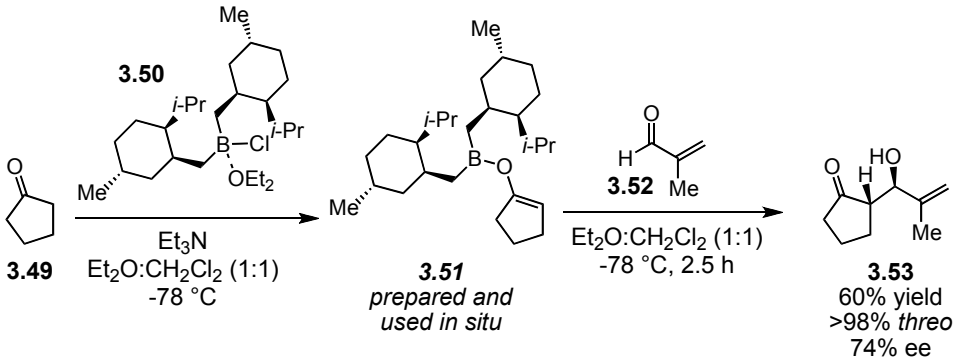
Several reports have described aldol addition of cyclopentanone-derived enolates to aryl or alkenyl-based aldehydes. While these methods could, in theory, be applied to the current system, significant alteration of the reported system would likely be required. The following section will briefly outline these disclosures as well as address any potential shortcomings.

Gennari and coworkers reported that aldol addition of chiral boron-derived enolate **3.51** to alkenyl based aldehyde **3.52** provided adduct **3.53** in 60% yield and 74% ee (>98% threo).[156] In related reactions of acyclic enolates and aliphatic aldehydes, good selectivities were observed (80-86% ee); however, the enolate must be generated through kinetic enolization with Et_3N and chiral boron reagent **3.50**. This method cannot used to prepare the enolate needed for the synthesis of clavirolide C (i.e. **3.31**) as kinetic enolization would provide the undesired regioisomeric enolate. Attempts were carried out to prepare the requisite boron enolate through reaction of the lithium enolate derived

(156) "The Rational Design of Highly Stereoselective Boron Enolates Using Transition-State Computer Modeling: a Novel, Asymmetric Anti Aldol Reaction for Ketones," Gennari, C.; Hewkin, C. T.; Molinar, F.; Bernardi, A.; Commotti, A.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1992**, *57*, 5173-5177.

from chiral enol silane **3.31** with Cy_2BCl, but complex mixtures of products were observed. Independently, Evans[157] and Kuwajima[158] have developed methods for synthesis of boron enolates by treatment of the corresponding silyl enol ethers with R_2BBr and R_2BOTf, respectively; however, these methods were specific to *Z*-enolates.

Scheme 3.12: Chiral Reagent-Controlled Aldol Addition

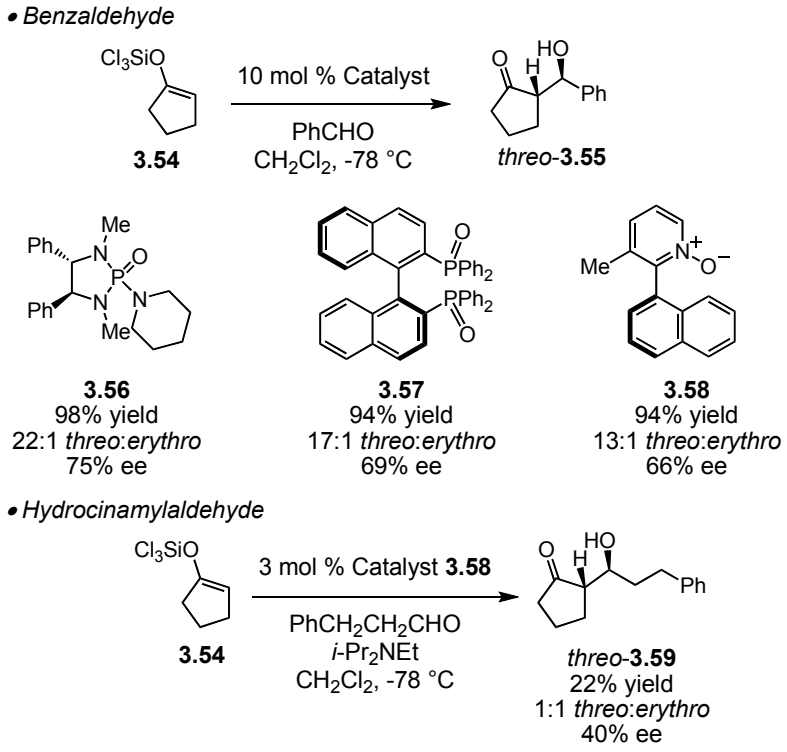


Chiral Lewis bases (i.e. **3.56**-**3.58**) have been reported to be highly efficient and selective catalysts for aldol addition of cyclopentenone-derived trichlorosilyl enolate **3.54** to aromatic aldehydes (Scheme 3.13).[159] Related reactions with aliphatic-based aldehydes, however, are inefficient and non-selective; the only example reported is illustrated in Scheme 3.13.[159b] Aldol addition of enolate **3.54** to hydrocinamylaldehyde, promoted by 3 mol % catalyst **3.58**, provided **3.59** in 22% yield, 1:1 dr (*threo*:*erythro*)

(157) "Formation of (Z)-Dialkylboron Enolates from Enolsilane: Stereoconvergent Transmetallation and Diastereoselective Aldol Reactions," Duffy, J. L; Yoon, T. P; Evans, D. A. *Tetrahedron Lett.* **1995**, *36*, 9245-9248.
(158) "Stereo- and Regio-Controlled Aldol Synthesis," Kuwajima, I.; Kato, M.; Mori, A. *Tetrahedron Lett.* **1980**, *21*, 4291-4294.
(159) (a) "Asymmetric Aldol Additions Catalyzed by Chiral Phosphoramides: Electronic Effects of the Aldehyde Component," Denmark, S. E.; Stavenger, R. A.; Wong, K-T. *Tetrahedron* **1998**, *54*, 10389-10402. (b) "Enantioselective Aldol Reactions of Trichlorosilyl Enol Ethers Catalyzed by Chiral *N,N'*-Dioxides and Monodentate *N*-Oxides," Nakajima, M.; Yokota, T.; Saito, M.; Hashimoto, S. *Tetrahedron Lett.* **2004**, *45*, 61-64. (c) "Chiral Phosphine Oxide BINAPO as a Lewis Base Catalyst for Asymmetric Allylation and Aldol Reaction of Trichlorosilyl Compounds," Kotani, S.; Hashimoto, S.; Nakajima, M. *Tetrahedron*, **2007**, *63*, 3122-3132.

and 40% ee. Furthermore, preparation of the moisture-sensitive trichlorosilyl enolates (i.e. **3.54**) would be difficult especially when handling volatile and precious chiral intermediates.

Scheme 3.13: Chiral Lewis Base-Catalyzed Aldol Addition of Trichlorosilyl Enol Ethers



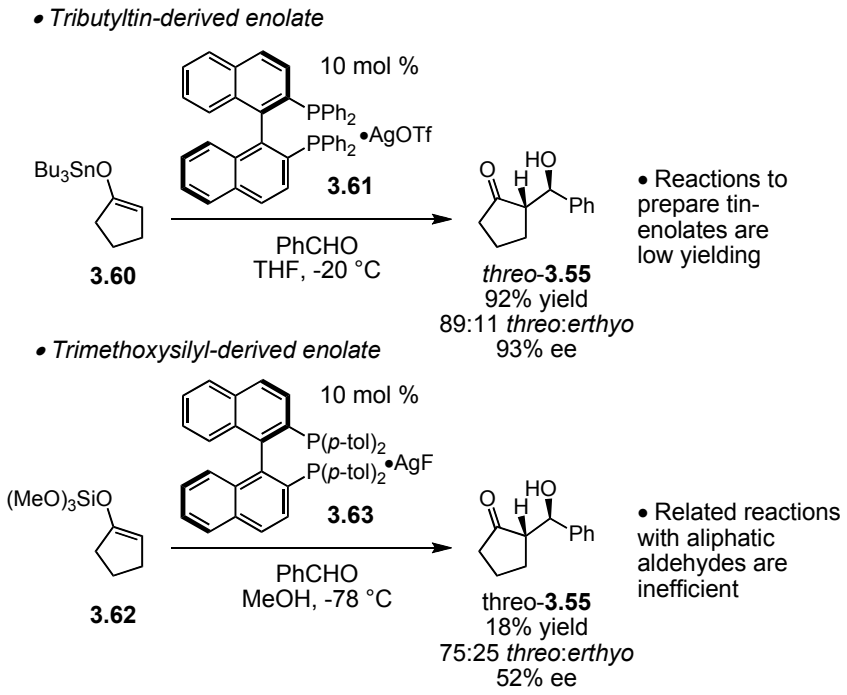
Yamamoto and coworkers have disclosed two methods for efficient and selective Ag-catalyzed aldol addition of tributyltin enolates (**3.60**)[160] as well as trimethoxysilyl enol ethers (**3.62**)[161] (Scheme 3.14). In the former system, high enantioselectivities were

(160) (a) "Enantioselective Aldol Reaction of Tin Enolates with Aldehydes Catalyzed by BINAP•Silver(I) Complex," Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319-9320. (b) "Asymmetric Aldol Reaction of Enol Trichloroacetate Catalyzed by Tin Methoxide and BINAP•Silver(I) Complex," Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8331-8339.

(161) "Catalytic Asymmetric Aldol Reaction of Trimethoxysilyl Enol Ethers Using 2,2'Bis(di-*p*-tolylphosphino)-1,1'binaphthyl•AgF Complex," Yanagisawa, A.; Nakatsuka, Y.; Asakawa, K.; Wadamoto, M.; Kageyama, H.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1477-1484.

observed for additions to aromatic aldehydes (93% ee, 89:11 dr, *threo:erythro*), and in related reactions of aliphatic-based aldehydes (*Z*-enolates as nucleophiles), the desired products were obtained in high yield and ee. Unfortunately, reactions to prepare the tin-enolates were low yielding (<60%) and cumbersome.[162] In situ preparation of the tin-enolate from the corresponding trichloroacetyl enol ether, and direct use in Ag-catalyzed asymmetric aldol reactions have been disclosed, however reactions of aliphatic aldehydes and cyclic silyl enol ethers were inefficient (<2% conv).[160b] In the latter system, enantioselective Ag-catalyzed aldol reactions with trimethoxysilyl enol ethers such as **3.62** led to inefficient reactions (18% yield, 52% ee, *threo:erythro*).[161]

Scheme 3.14: Enantioselective Ag-Catalyzed Aldol Additions



(162) "Stereoselective Aldol Condensations of Organotin Reagents with Aldehydes," Labadie, S. S.; Stille, J. K. *Tetrahedron* **1984**, *40*, 2329-2336.

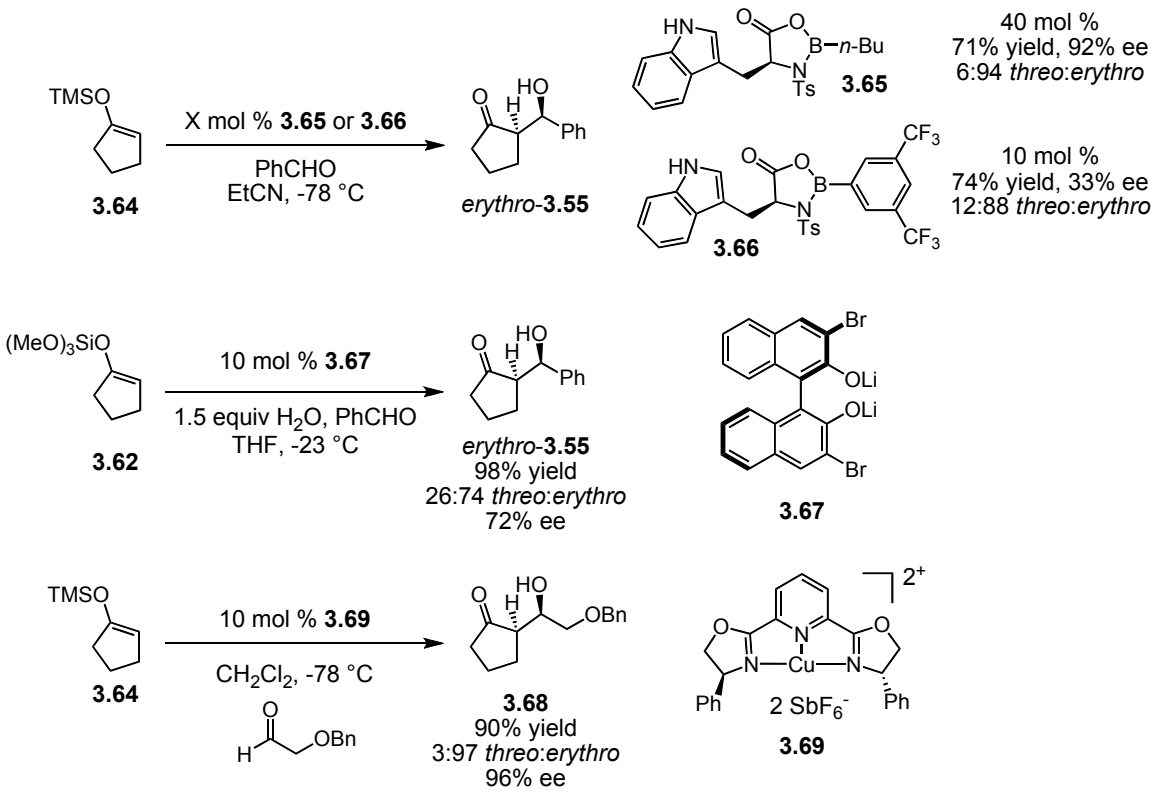
As illustrated in Scheme 3.15, several methods for catalytic enantioselective aldol additions that led to preferential formation of the *erythro* products have been reported.[163,164,165] High enantio- and diastereoselectivities have been observed for reactions with aromatic aldehydes as well as α-benzyloxyaldehydes (reactions with unsubstituted aliphatic-based aldehydes were not reported).[163a,164,165]

(163) (a) "Enantioselective Mukaiyama-Aldol and Aldol-Dihydropyrone Annulation Reactions Catalyzed by a Tryptophan-Derived Oxazaborolidine," Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907-6910. (b) "Scope and Limitations of Chiral *B*-[3,5-Bis(trifluoromethyl)phenyl]oxazaborolidine Catalyst for Use in the Mukaiyama Aldol Reaction," *J. Org. Chem.* **2000**, *65*, 9215-9218.

(164) "Enantioselective Aldol Reaction of Trimethoxysilyl Enol Ether Catalyzed by Lithium Binaptholate," Nakajima, M.; Orito, Y.; Ishizuka, T.; Hashimoto, S. *Org. Lett.* **2004**, *6*, 3763-3765.

(165) "C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Scope and Mechanism of Catalytic Enantioselective Aldol Additions of Enolsilanes to (Benzyloxy)acetaldehyde," Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669-685.

Scheme 3.15: Catalytic Enantioselective *Erythro*-Selective Aldol Reactions



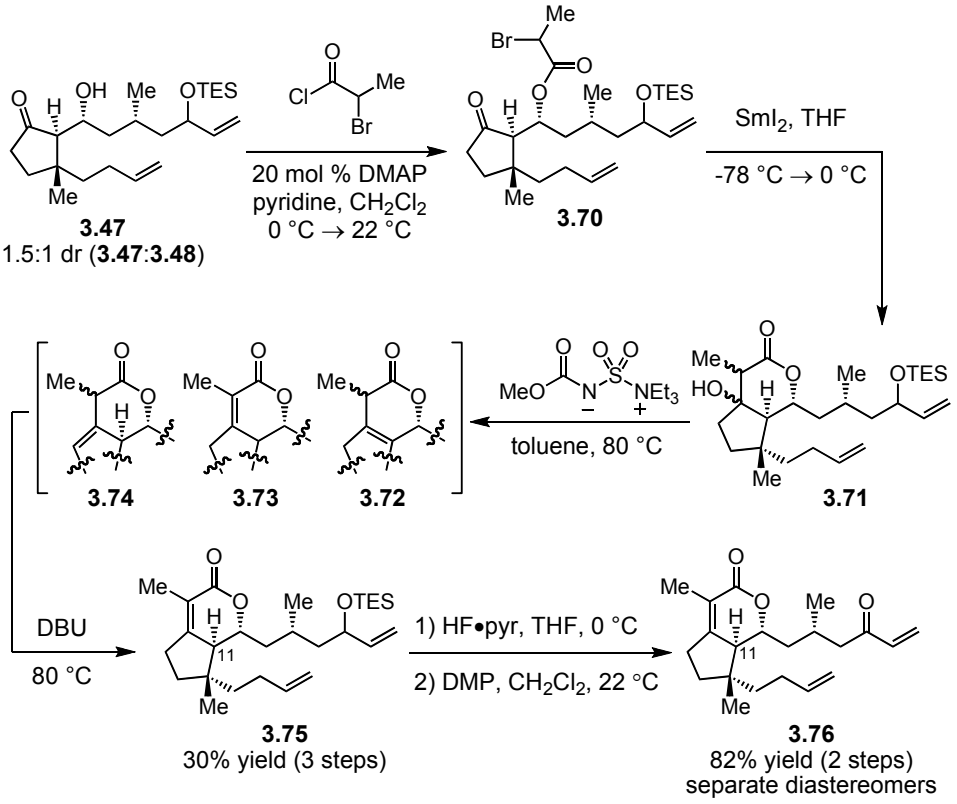
3.3.e Ring-Closing Metathesis Studies

Elaboration of β-hydroxy ketone **3.47** (1.5:1 **3.47**:**3.48**) was carried out in a straightforward manner (Scheme 3.16) in accordance with procedures reported by Wu[128a] and Xu.[128b-d] Esterification of secondary alcohol **3.47** with 2-bromopropionyl chloride, in the presence of pyridine and catalytic quantities of DMAP, provided **3.70**. Reformatsky-type aldol addition, mediated by SmI_2, delivered the tertiary alcohol **3.71** as an inconsequential mixture of diastereomers.[166] Elimination of the tertiary alcohol with

(166) "Investigations on 1,2-, 1,3, and 1,4-Asymmetric Induction in Intramolecular Reformatsky Reactions Promoted by Samarium (II) Iodide," Molander, G. A.; Etter, J. B.; Harring, L. A.; Thorel, P-J. *J. Am. Chem. Soc.* **1991**, *113*, 8036-8045.

Burgess reagent furnished a mixture of dehydrated products (**3.72**-**3.74**), which was isomerized to the desired α,β-unsaturated lactone **3.75** by treatment with DBU (54% yield over three steps). Desilylation with HF•pyr in THF at 0 ºC, followed by oxidation of the allylic alcohol with Dess-Martin periodinane (DMP), provided ketone **3.76** in 82% yield over two steps. At this stage, diastereomers, generated through the aldol addition, were readily separated by silica gel chromatography.

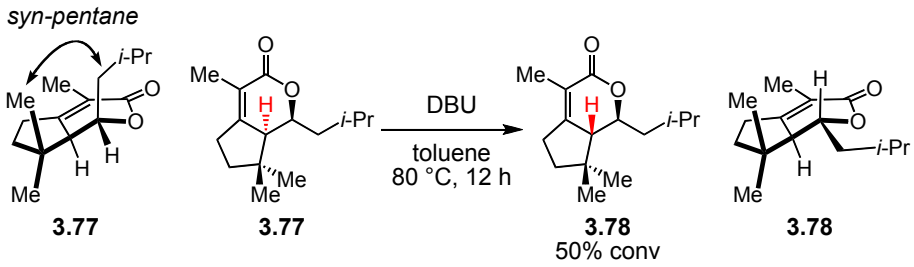
Scheme 3.16: Synthesis of Diene **3.76**



As an interesting corollary, isomerization of tetrasubstituted olefin **3.72** is stereospecific as only a single diastereomer at C11 of **3.75** was generated upon treatment with DBU (Scheme 3.16). We have been able take advantage of this observation by

demonstrating that the *erythro*-diastereomer **3.77**, which was destabilized by an unfavorable *syn*-pentane interaction, could be converted to the *threo*-diastereomer **3.78** upon treatment with DBU (Scheme 3.17). Therefore, it may be possible to carry out an *erythro*-selective aldol addition (Scheme 3.15) and epimerize the stereogenic center to afford the correct diastereomer at a later stage in the synthesis.

Scheme 3.17: Thermodynamic Preference for the *threo*-Diastereomer

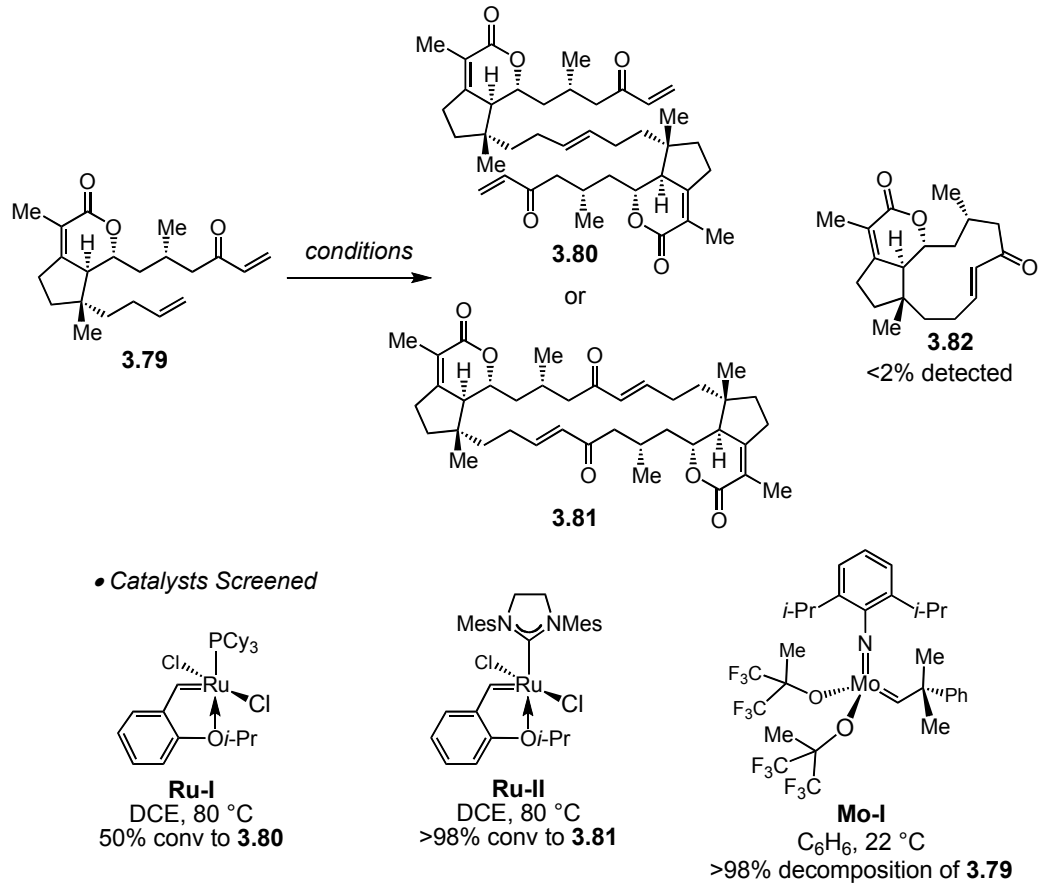


With ample quantities of **3.76** in hand, we were ready to investigate ring-closing metathesis to form 11-membered ring **3.82**; successful completion of this transformation would provide material one step from clavirolide C. As shown in Scheme 3.18, subjection of diene **3.76** to either Ru-catalyst **Ru-I**[167a] or **Ru-II**[167b] led to exclusive formation of cross-metathesis dimer **3.80** or 22-membered ring head-to-tail dimer **3.81**, respectively (<2% of the desired 11-membered ring **3.82** detected). Reactions carried out at higher temperatures (120 °C) and at high dilution (0.1 mM) led to decomposition of the substrate and/or ring-closed products. Attempted RCM of **3.79**, promoted by Mo-

(167) (a) "A Recyclable Ruthenium(II) Metathesis Catalyst," Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791. (b) "Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts," Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179. (c) For review, see: "Ru Complexes Bearing Bidentate Carbenes: From Innocent Curiosity to Uniquely Effective Catalyst for Olefin Metathesis," Hoveyda, A. H.; Gillingham, D. G; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2002**, *2*, 8-23.

based catalyst **Mo-I**,[168] failed completely, likely due to the incompatibility of the Lewis basic carbonyl functionalities present in **3.76** with the highly Lewis acidic Mo(VI) catalyst.[169]

Scheme 3.18: Studies Towards Attempted Ring-Closing Metathesis (RCM) of Diene **3.79**



(168) (a) "Synthesis of Molybdenum Imido Alkylidene Complexes and Some Reactions Involving Acyclic Olefins," Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 375-3886. For a review, see: (b) "Molybdenum and Tungsten Imido Alkylidene Complexes as Efficient Olefin-Metathesis Catalysts," Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592-4633.

(169) "Hydroxyl-Directed Stereoselective Olefination of Ketones by Transition Metal Alkylidenes," Fujimura, O.; Fu, G. C.; Rothemund, P. W. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2355-2356.

While the utility of catalytic RCM with well-defined catalysts is established, the effectiveness of these protocols for the synthesis of medium rings (9-11) is not well precedented due to the high strain associated with these ring sizes.[170,171] Typically, high dilution, temperature and catalyst loading are necessary to realize effective ring closure. Select examples where 11-membered rings have been prepared by catalytic RCM, en route to natural products, are illustrated in Figure 3.3.[172,173]

(170) For reviews regarding the utility of olefin metathesis in synthesis, see: (a) "Synthesis of Medium-Sized Rings by the Ring-Closing Metathesis Reaction," Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073-2077. (b) "Metathesis Reactions in Total Synthesis," Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490-2527. (c) "Macrocyclization by Ring-Closing Metathesis in the Total Synthesis of Natural Products: Reaction Conditions and Limitations," Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086-6101.

(171) "The Role of Ring Strain on the Ease of Ring Closure of Bifunctional Chain Molecules," Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117-3125.

(172) (a) "Ring Closing Metathesis and Cross Metathesis of Carbohydrate Derivatives," El Sukkari, H.; Gesson, J-P.; Renoux, B. *Tetrahedron Lett.* **1998**, *39*, 4043-4046. (b) "Design and Synthesis of Constrained Epothilone Analogs: The Efficient Synthesis of Eleven-Membered Rings by Olefin Metathesis," Winkler, J. D.; Holland, J. M.; Kasparec, J.; Axelsen, P. H. *Tetrahedron* **1999**, *55*, 8199-8214. (c) "Ring Expansions of β-Keto Lactone with Zinc Carbenoids: Syntheses of (+)-Patulolide A and (+/-)-Patulolide B," Ronsheim, M. D.; Zercher, C. K. *J. Org. Chem.* **2003**, *68*, 1878-1885. (d) "Total Synthesis of Coleophomones B, C, and D," Nicolaou, K. C.; Montagnon, T.; Vassilikogiannakis, G.; Mathison, C. J. N *J. Am. Chem. Soc.* **2005**, *127*, 8872-8888. (e) "Total Synthesis of Aspercyclide C," Fürstner, A.; Müller, C. *Chem. Commun.* **2005**, 5583-5585. (f) "Studies on Ring-Closing Metathesis for the Formation of the 11-Membered Ring System of Daphnezomine C," Tanabe, K.; Fujie, A.; Ohmori, N.; Hiraga, Y.; Kojima, S.; Ohkata, K. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1597-1604.

(173) For other examples where 11-membered rings have been prepared by RCM, see: (a) "Silicon Tethered Ring-Closing Metathesis Reactions for Self- and Cross-Coupling of Alkenols," Hoye, T. R.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429-1432. (b) "Ring-Closing Metathesis in the Synthesis of Large and Medium-Sized Oxacycles. Application to the Synthesis of Polyoxygenated Macrocycles," Delgado, M.; Martín, J. D. *J. Org. Chem.* **1999**, *64*, 4798-4816. (c) "Concise Synthesis of Azacycloundecenes using Ring-Closing Metathesis," Arisawa, M.; Kato, C.; Kaneko, H.; Nishida, A.; Nakagawa, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1873-1876 (d) "A Novel Strategy for the Synthesis of Medium-Sized Lactams," Bieräugel, H.; Jansen, T. P.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Org. Lett.* **2002**, *4*, 2673-2674. (e) " Diversity-Oriented Synthesis of Azaspirocycles," Wipf, P.; Stephenson, C. R. J.; Walcak, M. A. A. *Org. Lett.* **2004**, *6*, 3009-3012. (f) "Asymmetric Modular Synthesis of Highly Functionalized Medium-Sized Carbocycles and Lactones via Ring-Closing Metathesis of Sulfoximine-Substituted Trienes," Lejkowski, M.; Gais, H-J.; Banerjee, P.; Vermeeren, C. *J. Am. Chem. Soc.* **2006***, 128*, *128*, 15378-15379.

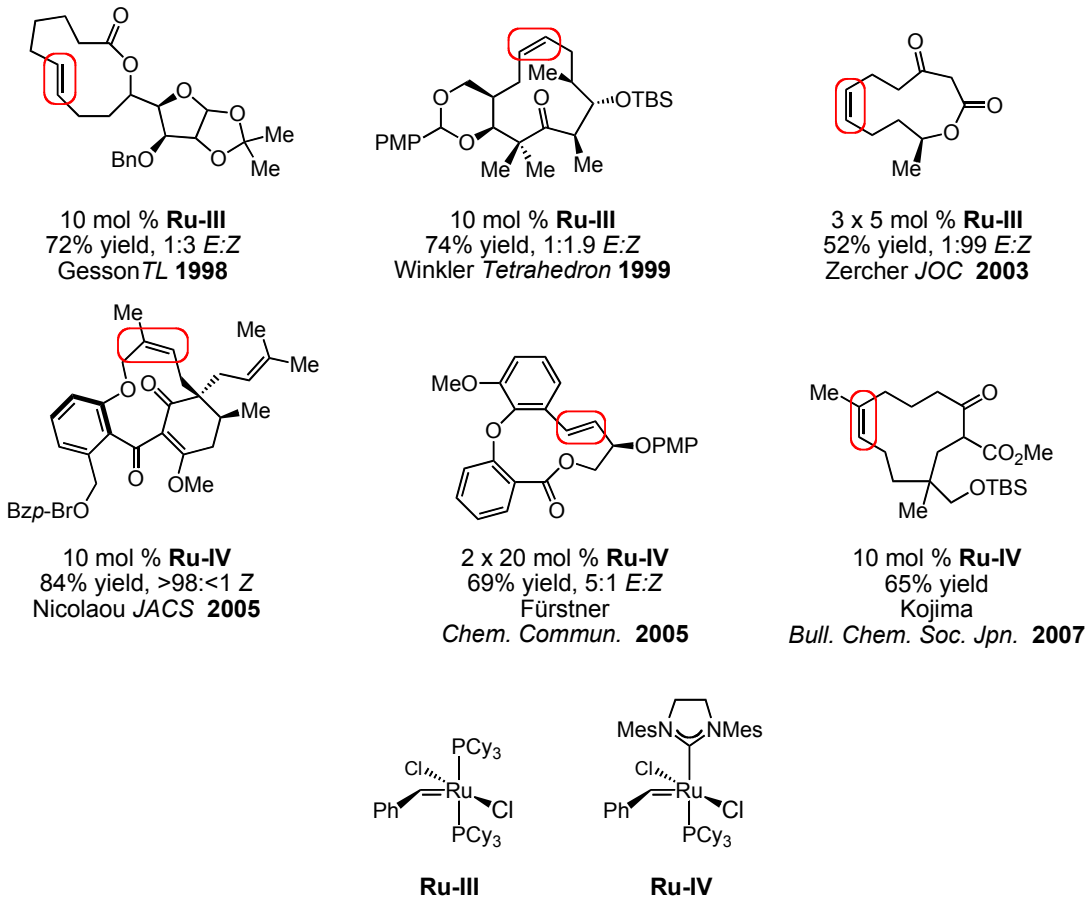


Figure 3.3: Select Examples of RCM to Prepare 11-Membered Rings in Natural Product Synthesis

At this point in our studies, we decided to investigate this transformation by and evaluating potential metathesis products with carrying out high-level calculations of ring strain.[174] As illustrated in Figure 3.4, the calculated ring strain of **3.82** is ~10 kcal/mol,

(174) Conformational searches were performed in Spartan '04 with PM3 semi-empirical method. "Q-Chem 2.0: A High-Performance *ab initio* Electronic Structure Program Package," Kong, J.; White, C. A.; Krylov, A. I.; Sherrill, C. D.; Adamson, R. D.; Furlani, T. R.; Lee, M. S.; Lee, A. M.; Gwaltney, S. R.; Adams, T. R.; Ochsenfeld, C.; Gilbert, A. T. B.; Kedziora, G. S.; Rassolov, V. A.; Maurice, D. R.; Nair, N.; Shao, Y.; Besley, N. A.; Maslen, P. E.; Dombroski, J. P.; Daschel, H.; Zhang, W.; Korambath, P. P.; Baker, J.; Byrd, E. F. C.; VanVoorhis, T.; Oumi, M.; Hirata, S.; Hsu, C. –P.; Ishikawa, N.; Florian, J.; Warshel, A.; Johnson, B. G.; Gill, P. M. W.; Head-Gordon, M.; Pople, J. A. *J. Computational Chem.* **2000**, *21*, 1532. All promising conformers were imported into Gaussian 03. Stationary points on the potential energy surface were calculated with Gaussian 03.D02 suite. Throughout the studies B3LYP density functional was used.

which, as demonstrated, was prohibitively high for effective ring-closure in this case. Replacement of the enone unit with an allylic alcohol leads to a less strained system of ~8-9 kcal/mol (compare **3.83** and **3.82**, Figure 3.4). Furthermore, the lactone moiety contributes ~2 kcal/mol of ring strain, as illustrated by calculations of **3.84**.

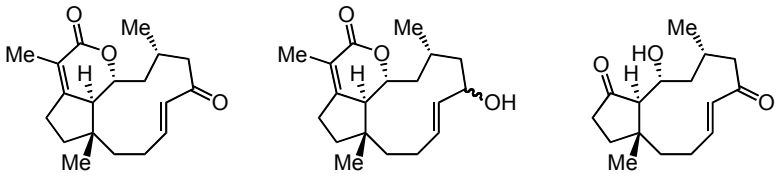


Figure 3.4: Ring Strain Energies of Various RCM Products

Armed with a better understanding of what structural features contribute to ring strain, we set out to test these substrates in catalytic RCM reactions. As illustrated in Scheme 3.19, subjection of **3.75a** or **3.75b** to a variety of RCM conditions led to only decomposition of the substrate and/or product; however, when diene **3.85** (prepared in two steps from **3.47**)[175] was subjected to a refluxing solution of **Ru-II** in CH_2Cl_2, the

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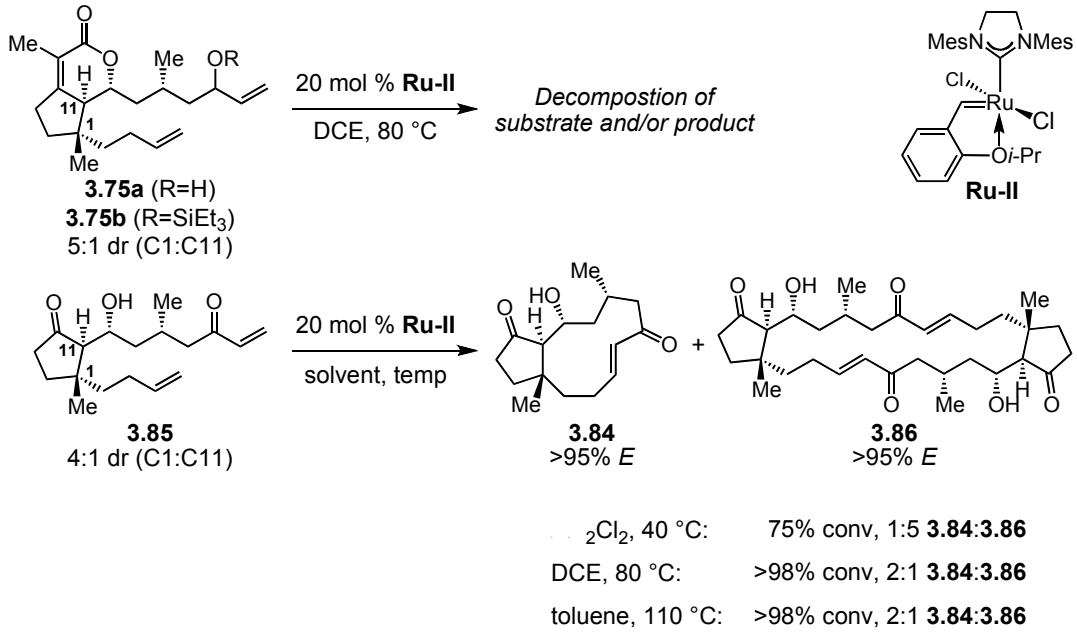
The electronic configurations of the molecular systems were described by 6-31G(d,p) double-ζ basis set on H, C, and O; the basis set for O was augmented with a single *sp*-type and a single *d*-type diffuse functions. All basis sets are as supplied by Gaussian 03.D02 suite. The minima were confirmed by frequency calculation at the same level of theory. Gaussian 03, revision D02: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

(175) 1) HF•pyr, THF, 0 °C, 2) MnO_2, Et_2O, 22 °C: 34% yield (2 steps), see Experimentals section for details.

desired 11-membered ring **3.84** (confirmed through X-ray crystal structure analysis)[176] was observed as a minor constituent of the reaction mixture. The remainder of the unpurified mixture contained 22-membered ring head-to-tail dimer **3.86**. The ratio of **3.84**:**3.86** could be increased to 2:1 when the reaction was carried out at higher temperatures (80-120 °C), however, the unpurified reaction mixture was complex. It is important to note, that while we did obtain 11-membered ring product **3.84** in these reactions, significant optimization would be required in order to provide sufficient quantities of material for later stages of the synthesis. Therefore, we continued substrate optimization.

Scheme 3.19: Catalytic RCM of Dienes **3.75** and **3.85**.



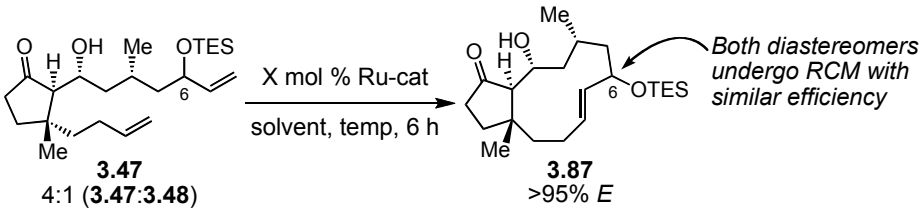
(176) This crystal structure was found to exist as a mixture of two interconverting enone conformers, *s-cis* and *s-trans*.

Based on the strain energies depicted in Figure 3.4, 11-membered ring **3.87** (Table 3.4), which combines the strain releasing features of **3.83** and **3.84**, would likely be the least strained system. *Indeed, RCM of **3.47** (4:1 **3.47**:**3.48**)[177] in DCE at 83 °C, promoted by 20 mol % **Ru-II**, led to formation of the desired product **3.87** in 73% isolated yield (>95% E, Table 3.4, entry 3).* Reactions at lower temperatures (22 or 40 °C) led to low conversion of **3.47** (Table 3.4, entries 1 and 2). Interestingly, both diastereomers of **3.47** at C6 underwent macrocyclization with similar efficiency while diastereomer **3.48** underwent oligomerization. Further optimization established that slow addition of diene **3.47** (4:1 **3.47**:**3.48**) to a refluxing solution of Ru-catalyst, a modification that we surmised would reduce competitive oligomerization of starting diene **3.47**, led to increased yields of isolated ring-closed product **3.87** (Table 3.4, compare entries 3 and 4). Catalyst loading could also be reduced to 5 mol % with minimal loss in isolated yield of **3.87** (Table 3.4, entry 5). It should be noted, however, that rigorously anhydrous conditions were required to achieve >98% conv with 5 mol % **Ru-II**; reactions carried out with 20 mol % **Ru-II** could be used to observe >98% conv without adherence to such strict guidelines. Furthermore, olefin metathesis promoted by **Ru-IV** under the optimal conditions for **Ru-II**[178] led to <10% conv (Table 3.4, entry 7). The low conversion observed with reaction promoted by **Ru-IV** is likely due the thermal instability associated with this catalyst.[178] Catalytic ring-closing metathesis promoted by

(177) The diastereomeric ratio was increased from 1.5:1 **3.47**:**3.48** to 4:1 by partial separation of diastereomers by silica gel column chromatography.
(178) "Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands," Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.

sterically and electronically modified Ru-based catalysts **Ru-V** and **Ru-VI** provided the desired macrocyclic in comparable yields to reactions with **Ru-II** (Table 3.4, entries 8-9**)**. Ironically, diene **3.47** was the first to be prepared, however, the last to be considered as a potential RCM substrate. It is important to note that catalytic RCM of the parent allylic alcohol failed to deliver the desired product and only led to decomposition of the substrate and/or product. It has been established that Ru-based olefin metathesis catalysts are unstable in the presence of allylic alcohols.[179]

Table 3.4: RCM of Diene **3.47**

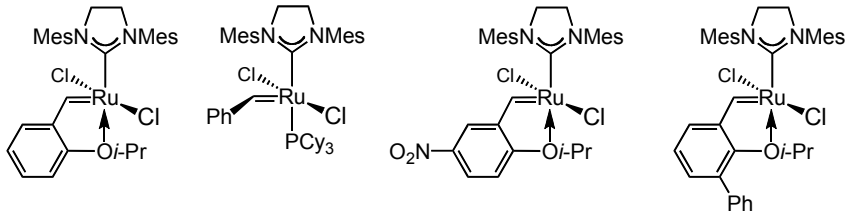


3.47
4:1 (**3.47**:**3.48**)

3.87
>95% *E*

entry	catalyst	mol %	solvent	temp (°C)	slow addition[a]	yield (%)[b]
1	**Ru-II**	20	CH_2Cl_2	22	no	<10% conv
2	**Ru-II**	20	CH_2Cl_2	40	no	<10% conv
3	**Ru-II**	20	$Cl(CH_2)_2Cl$	83	no	73
4	**Ru-II**	20	$Cl(CH_2)_2Cl$	83	yes	85
5	**Ru-II**	10	$Cl(CH_2)_2Cl$	83	yes	68
6	**Ru-II**	5	$Cl(CH_2)_2Cl$	83	yes	75
7	**Ru-IV**	20	$Cl(CH_2)_2Cl$	83	yes	<10% conv
8	**Ru-V**	20	$Cl(CH_2)_2Cl$	83	yes	63
9	**Ru-VI**	20	$Cl(CH_2)_2Cl$	83	yes	86

[a] Slow addition of substrate over 3 h [b] Yield of isolated product



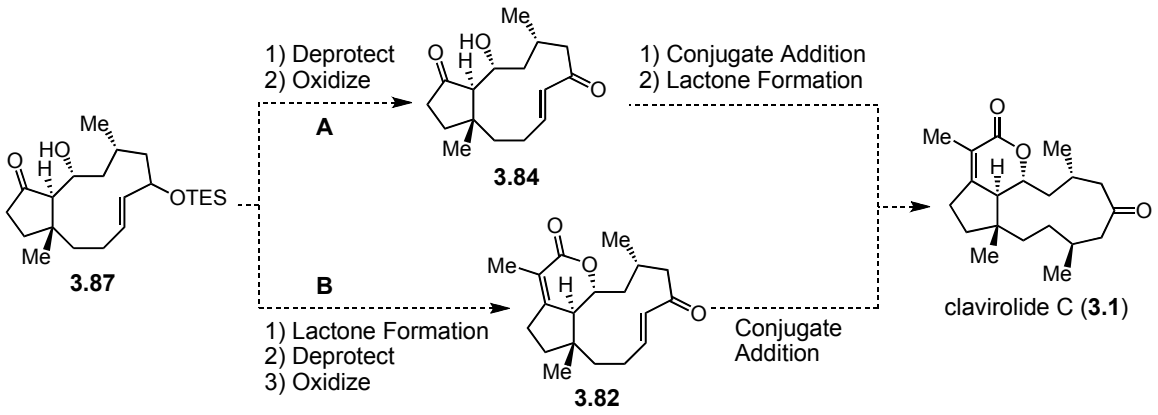
Ru-II **Ru-IV** **Ru-V** **Ru-VI**

(179) "Some Allylic Substituent Effects in Ring-Closing Metathesis Reactions: Allylic Alcohol Activation," Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123-1125.

3.3.f Completion of the Total Synthesis

Two possible endgame strategies are outlined in Scheme 3.20. Each route relies on the same set of transformations to convert **3.87** to clavirolide C **(3.1**). In route **A**, the enone unit is established first to afford **3.84**. Conjugate addition and lactone formation would provide the natural product. In route **B**, the order of transformations is reversed: installation of the lactone and enone moieties would afford **3.82**, which could undergo conjugate addition to afford the natural product. At the onset, it was difficult to ascertain which route should be pursed initially; such consideration can only be clarified through careful experimentation.

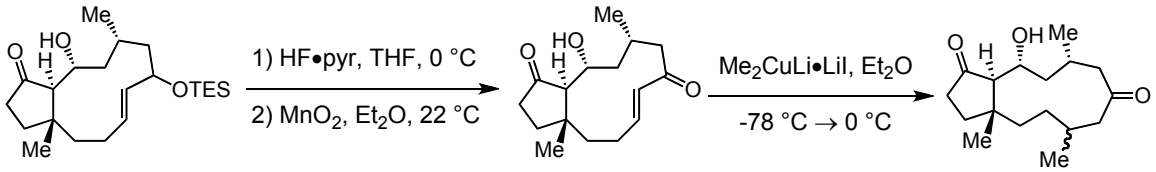
Scheme 3.20: Endgame Strategies



Enone **3.84** was readily prepared in 67% yield (two steps) by deprotection of silyl ether **3.87** with HF•pyr, followed by selective oxidation of the derived allylic alcohol with MnO_2 (Scheme 3.21). Conjugate addition to **3.84** with Me_2CuLi•LiI in Et_2O, however, led to a complex mixture of products. Purification of this mixture led to the isolation of two compounds (1:1) whose spectral data (^{1}H NMR, LRMS) were consistent with compound **3.88**. While, this sequence could be optimized to deliver sufficient

quantities of **3.88**, concomitant studies directed toward route **B** proved to be more promising.

Scheme 3.21: Route **A**



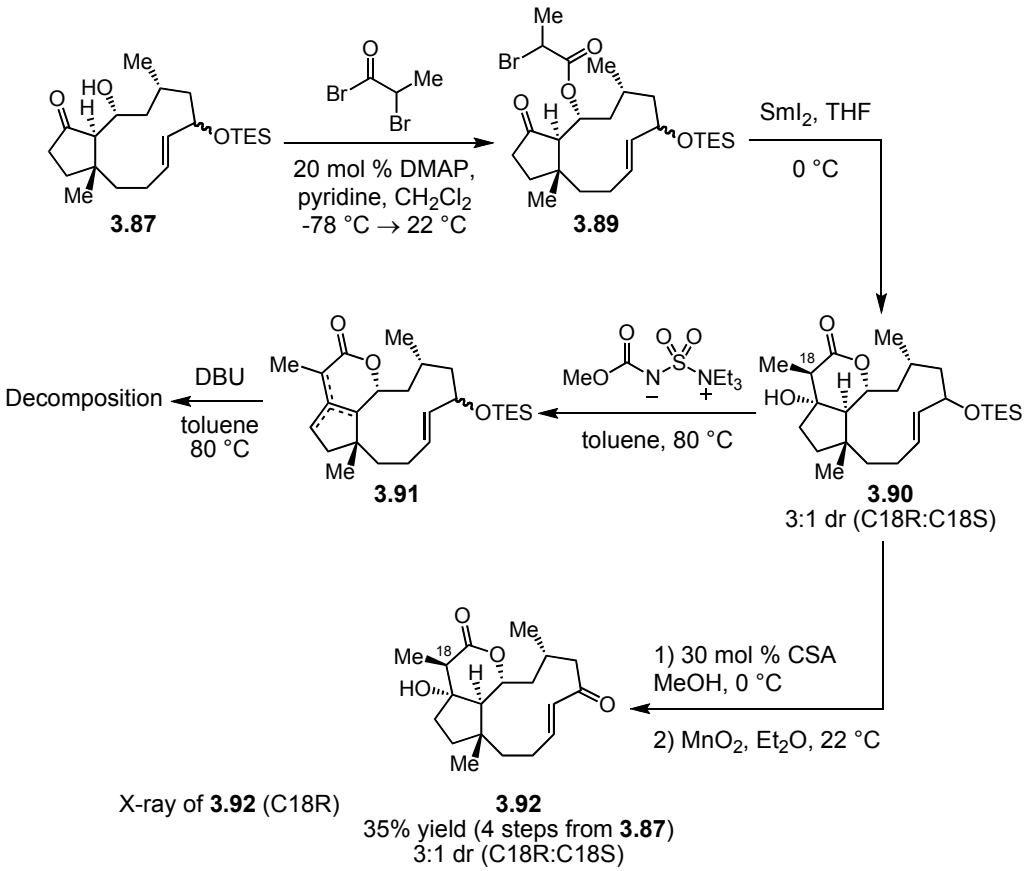
3.87

3.84
67% yield
for X-ray structure, see:
Scheme 3.19

3.88
complex mixture

The lactone ring was installed in analogy to previous studies (Scheme 3.16). Esterification of alcohol **3.87** with 2-bromopropionyl bromide, followed by SmI_2-mediated Reformatsky reaction, provided **3.90** (3:1 dr at C18, inconsequential to the total synthesis) in ~44% yield over two steps (Scheme 3.22). It is important to note that slow addition of SmI_2 (0.1M in THF) to a solution **3.89** was required to achieve optimal yield of isolated product (~70%); inverse addition delivered **3.90** in ~40% yield. Dehydration with Burgess reagent provided **3.91** as a mixture of olefin isomers; however, isomerization under previously identified optimal conditions (Scheme 3.16) led to decomposition of **3.91**. To circumvent the instability associated with **3.91**, deprotection of the silyl ether and oxidation with MnO_2 was carried out to provide **3.92** (confirmed by X-ray crystal structure analysis) in 35% yield from **3.87** (4 steps, 3:1 dr at C18, Scheme 3.22).

Scheme 3.22: Route **B**



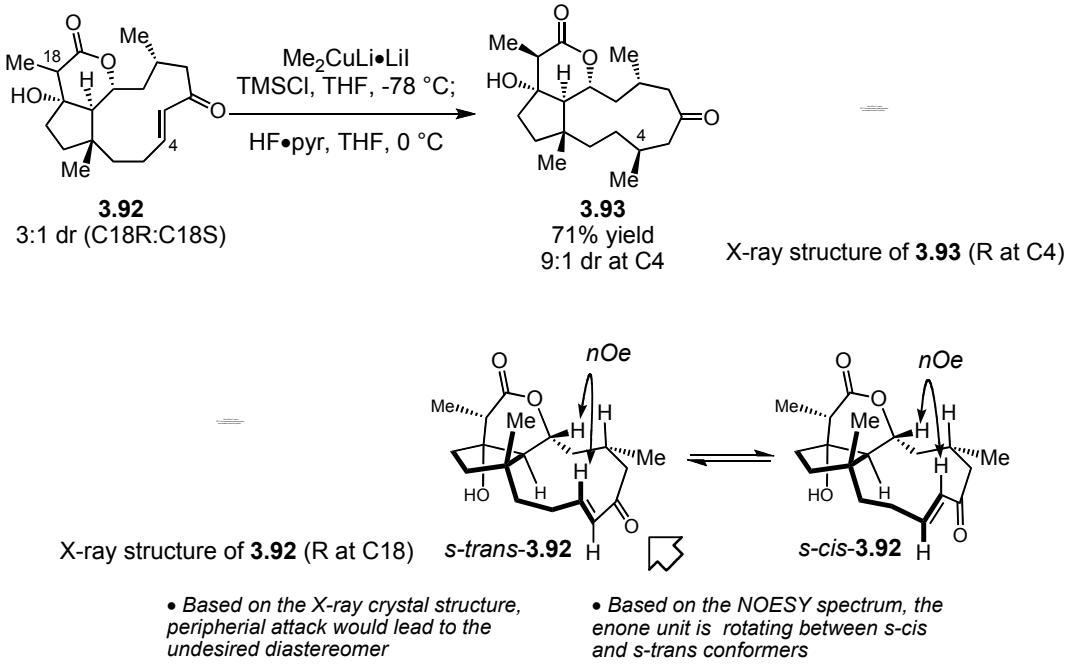
Conjugate addition of $Me_2CuLi{\bullet}LiI$ to **3.92**, in the presence of TMSCl, and subsequent deprotection of the derived silyl enol ether, led to clean formation of **3.93** in 71% yield (9:1 dr at C4, Scheme 3.23).[180] Based on the X-ray crystal structure of **3.92**, peripheral attack of the cuprate should give rise to the undesired diastereomer at C4;[181] however, the observed selectivity leads us to believe the *s-cis* conformation of the enone

(180) Since >98% conv was observed in a reaction that generates little of no impurities (as judged by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures), it appears that conjugate addition to the minor diastereomer of intermediate **3.92** also leads to desired product stereoisomer. Furthermore, epimerization of the stereogenic center at C18 must occur either during the reaction or upon workup. It is likely that the mixture of diastereomers is at C4 and not C18, because conversion of **3.93** to clavirolide C (**3.1)** delivered small quantities of *epi*-C4-clavirolide C as well, a known compound; see ref (126).

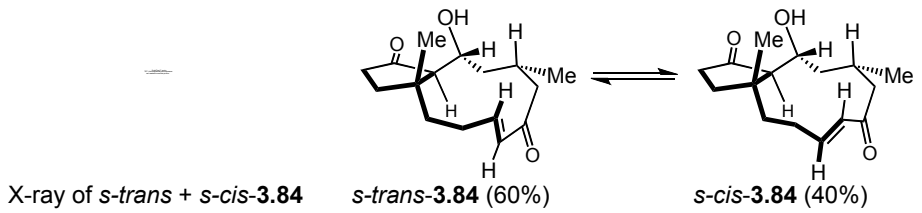
(181) For a discussion regarding the concept of peripheral attack, see: "Macrocycles in the Construction of Acyclic Stereochemistry," Still, W. C.; MacPherson, L. J.; Harada, T.; Callahan, J. F. *Tetrahedron* **1984**, *12*, 2275-2281.

undergoes conjugate addition more readily than the *s-trans*. This hypothesis requires that the enone be capable of interconversion between these two conformations. Indeed, analysis of the NOESY spectrum (400 MHz, $CDCl_3$) of **3.92** revealed that both olefinic protons were in close proximity with H10, likely due to facile rotation of the enone moiety (Scheme 3.23). High-level calculations[174] predicted that *s-trans*-**3.92** was ~2 kcal/mol lower in energy than *s-cis*-**3.92**, suggesting that both conformers could exist under standard conditions. In a closely related X-ray crystal structure (**3.84**), both *s-cis* and *s-trans* conformations were observed to exist in the crystalline state (60:40, *s-trans*:*s-cis*, Scheme 3.24).

***Scheme 3.23*:** Diastereoselective Conjugate Addition to **3.92**

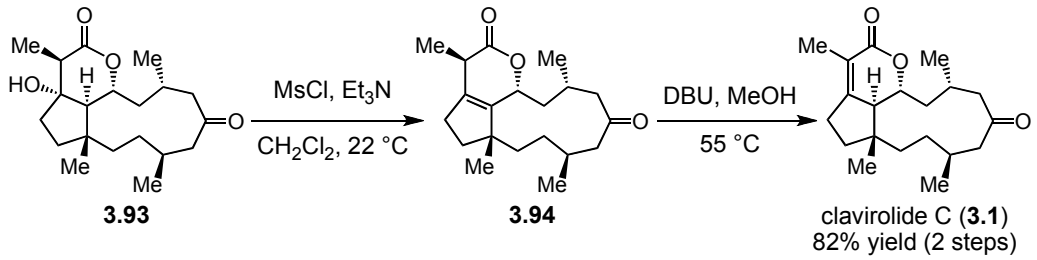


Scheme 3.24: X-Ray Crystal Structure of *S-Cis* and *S-Trans* Conformers



Completion of the total synthesis was carried out in a straightforward manner. Mesylation of **3.93** and spontaneous elimination furnished β,γ-unsaturated lactone **3.94**.[182] Isomerization of the olefin in **3.94** to the corresponding α,β-unsaturated lactone with DBU in MeOH furnished (-)-clavirolide C (**3.1**) in 82% yield. As observed previously, the isomerization was stereospecific, as the stereocenter at C11 was established with complete control.

Scheme 3.25: Completion of the Total Synthesis of Clavirolide C (**3.1**)



The enantioselective total synthesis of clavirolide C also serves to confirm the relative configuration of the molecule. The assignment was based on correlation with hydrogenation products of related of natural products clavulactone and clavirolide B (Figure 3.1) containing unsaturation at C3 and C4.

(182) Dehydration with Burgess reagent, followed by isomerization with DBU in toluene at 80 °C, led to a complex mixture of products.

3.4 *Conclusions*

The enantioselective total synthesis of clavirolide C has been accomplished in 17 steps (longest linear) in 3.5% overall yield. The total synthesis highlights the utility of chiral peptide-based ligand-promoted Cu-catalyzed ACA of dialkylzinc reagents to unsaturated lactones as well as phosphine-free Ru-catalyzed olefin metathesis. Furthermore, studies en route to clavirolide C have spawned the development of a new method for Cu-NHC-catalyzed ACA to afford all-carbon quaternary stereogenic centers.

3.5 *Experimentals*

General. Infrared (IR) spectra were recorded on a Nicolet 210 spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm). Spectra for clavirolide C were recorded on a Varian Unity INOVA 500 (125 MHz). High-resolution mass spectrometry were performed on a Micromass LCT ESI-MS (positive mode) or JEOL AccuTOF DART at

the Mass Spectrometry Facility, Boston College. Enantiomer ratios were determined by chiral GLC analysis (Alltech Associated Chiraldex GTA column (30 m x 0.25 mm) in comparison with authentic racemic materials. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Polarimeter.

Unless otherwise noted, all reactions have been carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 ^oC) and flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: toluene and benzene were purified through a copper oxide and alumina column; CH_2Cl_2 and Et_2O were purged with argon and purified by passage through two alumina columns. Tetrahydrofuran (Aldrich) was purified by distillation from sodium benzophenone ketal immediately prior to use unless otherwise specified. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Doe & Ingalls) in air.

Reagents and Catalysts:

Ag-complexes Ag-III[183]**, Ag-IV**[184] **and Ag-V**[184] were prepared by previously reported methods.

(183) "All-Carbon Quaternary Stereogenic Centers by Enantioselective Cu-Catalyzed Conjugate Additions Promoted by a Chiral N-Heterocyclic Carbene," Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097-1100.
(184) "Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers by Catalytic Asymmetric Conjugate Additions of Alkyl- and Arylaluminum Reagents to Five-, Six- and Seven-Membered Ring β-

Benzaldehyde was purchased from Aldrich and distilled from CaH_2 before use.

***n*-BuLi** (1.6 M in hexanes) was purchased from Strem and titrated before use.

(+)-Camphor sulfonic acid (CSA) was purchased from Aldrich and recrystallized from EtOAc prior to use.

Chloroform was purchased from Fisher and purified by distillation over $CaCl_2$ before use.

Chlorotrimethylsilane was purchased from Aldrich and distilled from CaH_2 prior to use.

Copper (I) iodide was purchased from Strem and purified prior to use.[185]

Copper (II) triflate was purchased from Aldrich and recrystallized from CH_3CN/Et_2O before use.[185]

Copper (I) triflate•toluene complex (2:1) (brown solid) was purchased from Aldrich (99.99%) and used as received.

Dess-Martin Periodinane was purchased from Atlantic SciTech**.**

1,8-Diazobicyclo[5.4.0]undec-7-ene (DBU) was purchased from Aldrich and distilled over KOH prior to use.

5,6-Dihydro-2*H*-pyran-2-one was purchased from Lancaster and distilled under reduced pressure (~0.5 mmHg) before use.

1,2-Dichloroethane was purchased from Aldrich and distilled CaH_2 prior to use.

Diiodoethane was purchased from Aldrich and purified by washing a solution of diiodoethane in Et_2O with saturated solution of Na_2SO_4 prior to use.[185]

Substituted Cyclic Enones," May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *in press*.

(185) *Purification of Laboratory Chemicals;* Armarego, W. L. F.; Perrin, D. D.; 1997

Diisobutylaluminum hydride (neat, reagent grade) was purchased from Aldrich and used as received.

Dimethylzinc (1.2 M in toluene) was purchased from Acros and used as received.

4-Dimethylaminopyridine (DMAP) was purchased from Advanced Chem Tech and used as received.

***N,O*-Dimethylhydroxylamine hydrochloride** was purchased from Aldrich and used as received.

Dimethylsulfoxide was purchased from Aldrich and distilled over CaH_2 under vacuum prior to use.

Hydrogen fluoride•pyridine (~70% HF, ~30% pyridine) was purchased from Aldrich and used as received.

Imidazole was purchased from Lancaster and used as received.

Manganese dioxide (activated) was prepared as previously reported.[186]

Methanesulfonyl chloride was purchased from Aldrich and distilled from P_2O_5 prior to use.

Methanol (extra dry with molecular sieves) was purchased from Aldrich and used as received.

Methyl lithium (1.6 M in Et_2O, low halide content) was purchased from Aldrich and titrated prior to use.

Oxalyl chloride was purchased from Aldrich and distilled prior to use.

Potassium carbonate was purchased from Aldrich and used as received.

(186) "194. A Synthesis of Vitamin A from Cyclohexanone," Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094-1111.

***iso*-Propylmagnesium chloride** (1.78 M in THF) was prepared from *i*-PrCl and $Mg^{(0)}$ and titrated prior to use.

Pyridine was purchased from Aldrich and purified by distillation over KOH before use.

Ru-catalyst Ru-I and Ru-II was purchased from Materia and purified by silica gel chromatography and recrystallization (CH_2Cl_2/pentane) prior to use.

Samarium (0) was purchased from Aldrich and used as received.

Triethylborane was purchased from Strem and used as received.

Triethylamine was purchased from Aldrich and distilled from CaH_2 prior to use.

Triethylchlorosilane was purchased from Lancaster and used as received.

Triethylsilyl trifluoromethanesulfonate was purchased from Lancaster and distilled under vacuum prior to use.

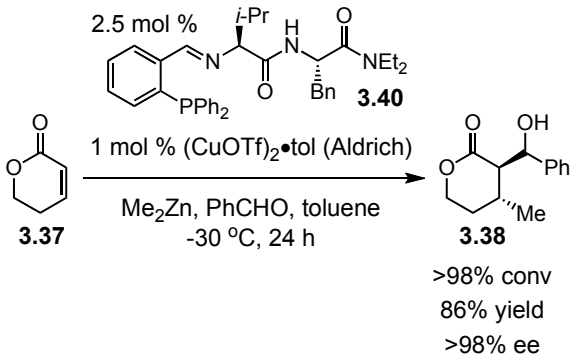
Trimethylaluminum was purchased from Strem and used as received. We have found that old bottles (>1 year) of Me_3Al were not as effective for the ACA reactions (conversions suffered, enantioselectivities remained unchanged).

Vinylmagnesium bromide was purchased from Aldrich and titrated prior to use.

(L,L)-Chiral Peptide Based Ligand 3.40 (Prepared in accordance to reported procedures).[187] **IR (neat):** 3378 (br w), 3271 (br w), 3054 (w), 2964 (w), 2931 (w), 2871

(187) "Modular Peptide-Based Phosphine Ligands in Asymmetric Catalysis: Efficient and Enantioselective Cu-Catalyzed Conjugate Additions to Five-, Six-, and Seven-Membered Cyclic Enones," Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755-756.

(w), 2242 (w), 1636 (s), 1495 (m), 1460 (m), 1433 (m), 1382 (w), 1260 (w), 1216 (w), 1095 (w), 1011 (s), 726 (s), 695 (s), 644 (m), 502 (m), 473 (m) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.60 (1H, d, *J* = 4.4 Hz), 7.97-7.93 (2H, m), 7.42 (1H, dt, *J* = 7.6, 1.2 Hz), 7.31-7.17 (15H, m), 6.90 (1H, ddd, *J* = 7.6, 4.4, 0.8 Hz), 5.15 (1H, q, *J* = 6.4 Hz), 3.54-3.45 (2H, m), 3.16 (1H, dd, *J* = 13.2, 8.8 Hz), 3.10-2.99 (4H, m), 2.15-2.07 (1H, m), 0.99 (3H, t, *J* = 6.8 Hz), 0.94 (3H, t, *J* = 7.2 Hz), 0.57 (3H, d, *J* = 6.8 Hz), 0.49 (3H, d, *J* = 6.8 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 171.9, 170.6, 161.9 (d, $J_{C\text{-}P}$ = 15.1 Hz), 138.8 (d, $J_{C\text{-}P}$ = 16.7 Hz), 137.8 (d, $J_{C\text{-}P}$ = 20.5 Hz), 137.0, 136.7 (d, $J_{C\text{-}P}$ = 7.2 Hz), 134.8, 134.6, 134.1, 133.9, 133.7, 130.8, 129.8, 129.2, 129.1, 128.9, 128.8, 128.8, 128.7, 128.7, 128.6, 127.0, 80.1, 49.9, 41.9, 40.7, 40.3, 32.8, 19.4, 17.2, 14.5, 13.1; **HRMS (ESI+):** Calcd for $C_{37}H_{43}N_3O_2P$ (M^++H): 592.30929 Found: 592.30684; **Optical Rotation:** $[\alpha]_D^{22}$ +52.5° (*c* 0.633, $CHCl_3$).

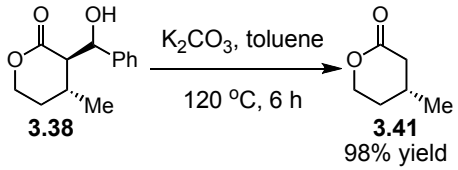


(3*R*,4*R*)-3-((*S*)-hydroxy(phenyl)methyl)-4-methyltetrahydro-2*H*-pyran-2-one 3.38.[188]

An oven-dried 500 mL round bottom flask was charged with **3.40** (295 mg, 0.500 mmol) and $(CuOTf)_2 \bullet C_6H_5CH_3$ (0.100 g, 0.200 mmol), weighed out under a N_2 atmosphere, was sealed with a septum and removed from the glove box. Toluene (65 mL) was added followed by 5,6-dihydro-2*H*-pyran-2-one (1.70 mL, 20.0 mmol) and benzaldehyde (4.05 μL, 40.0 mmol) to give an orange solution. The mixture was allowed to cool to –30 °C and Me_2Zn (50.0 mL, 1.20 M in toluene, 60.0 mmol) was added. The mixture was allowed to stir at –15 °C for 24 h at which time the reaction was quenched upon addition of saturated aqueous NH_4Cl (150 mL) then H_2O (150 mL). The aqueous layer was washed with EtOAc (2 x 100 mL) and the combined organic layers were washed with saturated aqueous solution of NH_4Cl (150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the pale yellow oil by silica gel column chromatography (30% Et_2O/petroleum ether to 80% Et_2O/petroleum ether, gradient) afforded **3.38** (3.85 g, 17.5 mmol, 87.5%) as a clear oil. Analyzed as a 1:1 mixture of diastereomers. **IR (neat):** 3427 (br s), 3072 (w), 3034 (w), 2957 (m), 2924 (m), 2875 (w), 2859 (w), 1717 (s), 1466 (m), 1400 (m), 1269 (m), 1231 (m), 1203 (m), 1089 (m), 1061 (m), 914 (w), 876 (w), 761 (w), 706 (s), 657 (w) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39-7.26 (10H, m), 5.25 (1H, dd, *J* = 6.8, 3.6 Hz), 4.94 (1H, t, *J* = 5.2 Hz), 4.31-4.25 (2H, m), 4.18-4.13 (1H, m), 4.04 (1H, td, *J* = 10.4, 2.0 Hz), 3.92 (1H, d, *J* = 4.8 Hz), 3.83 (1H, d, *J* = 6.4 Hz), 2.65 (1H, dd, *J* = 8.4, 3.6 Hz), 2.52 (1H, t, *J* = 6.4 Hz),

(188) "Highly Enantioselective Cu-Catalyzed Conjugate Additions of Dialkylzinc Reagents to Unsaturated Furanones and Pyranones: Preparation of Air-Stable and Catalytically Active Cu-Peptide Complexes," Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306-5310.

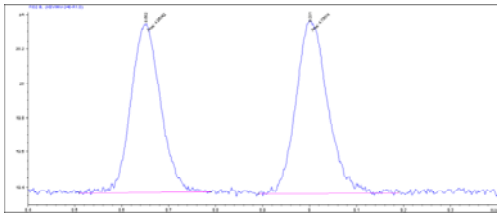
2.04-1.88 (3H, m), 1.83-1.76 (1H, m), 1.58-1.47 (2H, m), 0.82 (3H, d, J = 6.8 Hz), 0.76 (3H, d, J = 6.8 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 174.4, 174.1, 141.4, 141.3, 128.7, 128.6, 128.2, 128.1, 126.8, 126.5, 74.4, 73.7, 68.2, 66.8, 55.2, 54.6, 31.6, 31.1, 27.9, 27.2, 21.5, 21.3; **HRMS (ESI+):** Calcd for $C_{13}H_{16}O_3$: 220.1099 Found: 220.1099; Enantiomeric purity was determined after retro-aldol reaction (**3.38 → 3.41**).



(*R*)-4-Methyltetrahydro-2*H*-pyran-2-one 3.41.[188] To a solution of the conjugate addition adduct **3.38** (7.20 g, 32.7 mmol) in toluene (316 mL) was added K_2CO_3 (4.96 g, 36.0 mmol). The reaction vessel was equipped with a reflux condenser and the solution allowed to warm to 110 °C with a thermowell. After 2 h, the mixture was allowed to cool to 22 °C and loaded directly on a column containing silica gel. Purification by silica gel column chromatography (10% diethyl ether/petroleum ether to 100% diethyl ether, gradient) yielded **3.41** (3.70 g, 32.4 mmol, 99%) as a clear oil. **IR (neat):** 2958 (br m), 2929 (br w), 2874 (w), 1722 (s), 1457 (w), 1401 (m), 1255 (m), 1224 (s), 1152 (m), 1062 (s), 994 (s), 912 (m), 823 (m), 779 (m), 652 (m), 585 (m), 509 (m) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.41 (1H, ddd, J = 11.2 4.8, 3.6 Hz), 4.26 (1H, ddd, J = 10.8, 10.4, 3.6 Hz), 2.72-2.64 (1H, m), 2.15-2.05 (2H, m), 1.95-1.88 (1H, m), 1.57-1.47 (1H, m), 1.06 (3H, d, J = 6.4 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 171.4, 68.6, 38.3, 30.7, 26.6, 21.5;

HRMS (ESI+): Calcd for $C_6H_{11}O_2$ (M^++H): 115.0759, Found: 115.0759; **Optical Rotation:** $[\alpha]_D^{22}$ +22.8 (*c* 0.773, $CHCl_3$) for an enantiomerically enriched sample of >98% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material (>98% ee shown; chiral dex GTA column, 15 psi, 110 °C).



#	Time	Area	Height	Width	Area%
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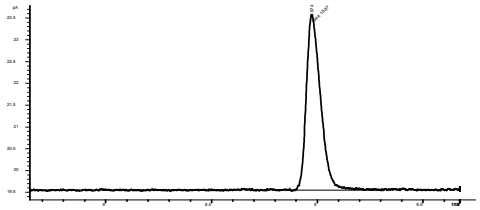
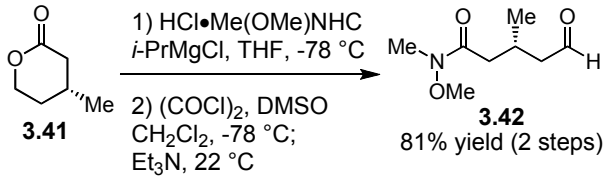
2	9.001	4.7	1E0	0.0785	52.468



#	Time	Area	Height	Width	Area%
1	--				
2	8.974	18.9	4	0.078	100.000

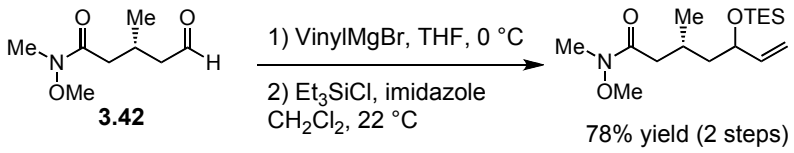


(*R*)-*N*-Methoxy-*N*,3-dimethyl-5-oxopentanamide (3.42). To a solution of lactone **3.41** (1.27 g, 11.1 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (3.25 g, 33.3 mmol) in tetrahydrofuran (50 mL) at 0 °C was added *i*-PrMgCl (37.4 mL, 1.78 M in THF, 66.6 mmol) through a syringe over five minutes. The mixture was allowed to warm to 22 °C and stir for 30 minutes. At this time, the reaction mixture was allowed to cool 0 °C and

quenched upon addition of a saturated aqueous solution of NH_4Cl (50 mL). The mixture was washed with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 1.94 g of the desired product as pale yellow oil. This material was used directly in the subsequent transformation without further purification.

To a solution of dimethylsulfoxide (1.63 mL, 23.0 mmol) in CH_2Cl_2 (96 mL) at – 78 °C was added oxalyl chloride (1.69 mL, 20.0 mmol). The mixture was allowed to stir for 15 minutes before the Weinreb amide (1.74 g of the above material, 10.0 mmol) was added by cannula as a solution in CH_2Cl_2 (10 mL). Additional CH_2Cl_2 (5 mL) was used to quantitate the transfer. After 30 minutes, triethylamine (9.88 mL, 70.4 mmol) was added by a syringe and the mixture allowed to warm to 22 °C and stir for 30 minutes. The reaction was quenched upon addition of H_2O (100 mL) and washed with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the yellow oil by silica gel column chromatography (10% EtOAc/petroleum ether to 50% EtOAc/petroleum ether, gradient) yielded **3.42** (1.40 g, 8.09 mmol, 80.9 % over two steps) as a clear oil. **IR (neat):** 2962 (m), 2939 (w), 2824 (w), 2725 (w), 1720 (s), 1655 (s), 1462 (m), 1385 (m), 1338 (m), 1178 (w), 1123 (w), 940 (m) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.75 (1H, t, *J* = 2.4 Hz), 3.67 (3H, s), 3.17 (3H, s), 2.63 (1H, sep, *J* = 7.2 Hz), 2.54 (1H, ddd, *J* = 16.0, 5.6, 1.6 Hz), 2.41 (2H, d, *J* = 6.8 Hz), 2.32 (1H, ddd, *J* = 16.4, 7.2, 2.4 Hz), 1.05 (3H, d, *J* = 6.4 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 202.2, 173.1, 61.3, 50.5, 38.4, 32.1, 25.0, 20.6; **HRMS**

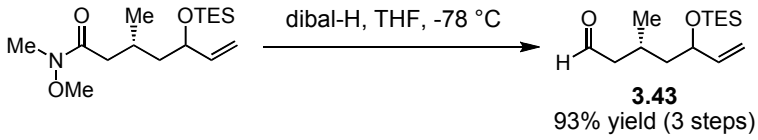
(ESI+): Calcd. for $C_8H_{16}NO_3$ (M^++H): 174.11302, Found: 174.11308; **Optical Rotation:** $[\alpha]_D^{22}$ –7.98 (*c* 1.01, $CHCl_3$).



(*R*)-*N*-Methoxy-*N*,3-dimethyl-5-(triethylsilyloxy)hept-6-enamide. To a solution of aldehyde **10** (2.24 g, 12.9 mmol) in tetrahydrofuran (64 mL) at 0 °C was added vinylmagnesium bromide (11.9 mL, 1.14 M in THF, 13.5 mmol) over five minutes through a syringe. After 15 minutes the reaction was quenched upon addition of a saturated aqueous solution of NH_4Cl (50 mL) and H_2O (50 mL). The mixture was washed with CH_2Cl_2 (2 x 50 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting material was used directly in the subsequent transformation without further purification.

To a solution of the above alcohol (~12.9 mmol) and imidazole (1.14 g, 16.7 mmol) in CH_2Cl_2 (200 mL) was added Et_3SiCl (2.33 mL, 15.5 mmol) by a syringe. After 30 minutes the reaction was quenched upon addition of a saturated aqueous solution of NH_4Cl (50 mL). The mixture was washed with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were washed with brine (100 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the clear oil by silica gel column chromatography (10% EtOAc/petroleum ether to 30% EtOAc/petroleum ether,

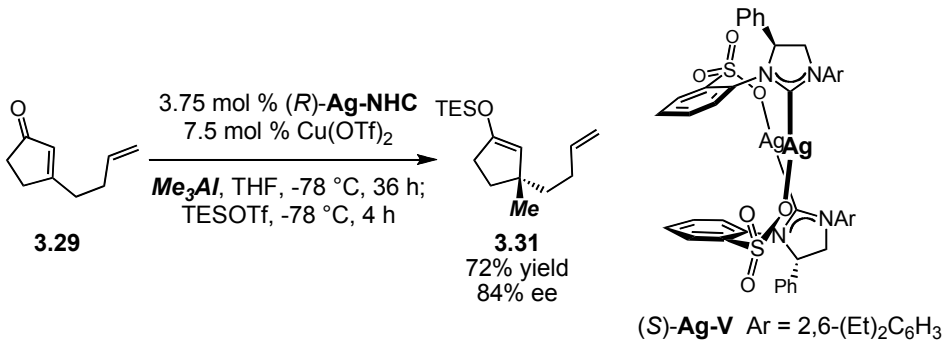
gradient) yielded the desired product (3.15 g, 10.0 mmol, 77.5% over two steps) as a clear oil. Analyzed as a 1:1 mixture of 3-(*R*), 5-(*R*) and 3-(*R*), 5-(*S*) diastereomers. **IR (neat):** 2954 (m), 2911 (m), 2876 (m), 1666 (s), 1459 (m), 1413 (m), 1380 (m), 1337 (w), 1238 (w), 1076 (m), 1003 (s), 921 (m), 740 (s), 725 (s) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.80 (2H, apt dddd, *J* = 16.8, 10.4, 6.4, 6.4 Hz), 5.14 (2H, apt dd, *J* = 17.2, 0.8 Hz), 5.06-5.00 (2H, m), 4.19-4.13 (2H, m), 3.66 (3H, s), 3.66 (3H, s), 3.17 (3H, s), 3.17 (3H, s), 2.45-2.38 (2H, m), 2.30-2.04 (4H, m), 1.61-1.40 (3H, m), 1.31 (1H, ddd, *J* = 13.2, 7.6, 4.8 Hz), 0.97-0.92 (24H, m), 0.59 (12H, q, *J* = 7.6 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 173.9, 142.1, 141.4, 114.4, 113.8, 72.6, 72.1, 61.2, 45.6, 45.4, 39.7, 39.4, 32.2, 26.5, 26.3, 20.3, 20.1, 6.9, 5.1, 5.0; **HRMS (ESI+):** Calcd. for $C_{16}H_{34}NO_3Si$ (M^++H): 316.23079, Found: 316.23105; **Optical Rotation:** $[\alpha]_D^{22}$ 0.00 (*c* 1.36, $CHCl_3$).



3.43
93% yield (3 steps)

(*R*)-3-Methyl-5-(triethylsilyloxy)hept-6-enal (3.43). To a solution of the Weinreb amide (1.35 g, 6.00 mmol) dissolved in tetrahydrofuran (60 mL) at –78 °C was added dibal-H (2.13 mL, 12.0 mmol). After 30 min, the reaction was quenched upon addition of a saturated aqueous solution of sodium potassium tartrate (50 mL) and allowed to stir at 22 °C for 1 h. At this time, the mixture was diluted with Et_2O (50 mL) and the aqueous layer separated. The organic layer was washed again with a saturated aqueous

solution of sodium potassium tartrate (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the clear oil by silica gel chromatography (100% petroleum ether to 10% Et_2O/petroleum ether, gradient) yielded **3.43** (1.42 g, 5.55 mmol, 92.5%) as a clear oil. Analyzed as a 1:1 mixture of 3-(*R*), 5-(*R*) and 3-(*R*), 5-(*S*) diastereomers. **IR (neat):** 2953 (m), 2911 (m), 2876 (m), 2711 (s), 1726 (s), 1459 (w), 1414 (w), 1379 (w), 1238 (w), 1073 (m), 1005 (s), 922 (m), 837 (w), 739 (s), 724 (s) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.73 (2H, t, *J* = 2.4 Hz), 5.83-5.74 (2H, m), 5.18-5.12 (2H, m), 5.08-5.01 (2H, m), 4.19-4.13 (2H, m), 2.51-2.38 (2H, m), 2.29-2.13 (4H, m), 1.57-1.42 (3H, m), 1.31 (1H, ddd, *J* = 13.6, 8.0, 4.4 Hz), 1.00-0.92 (24H, m), 0.62-0.55 (12H, m); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 202.7, 202.6, 142.4, 142.0, 114.6, 114.2, 72.3, 72.1, 51.5, 51.1, 45.4, 41.1, 24.8, 24.7, 20.6, 20.1, 7.0, 5.1, 5.1; **HRMS (ESI+):** Calcd. for $C_{14}H_{29}O_2Si$ (M^++H): 257.19368, Found: 257.19320; **Optical Rotation:** $[\alpha]_D^{22}$ +17.9 (*c* 1.07, $CHCl_3$).



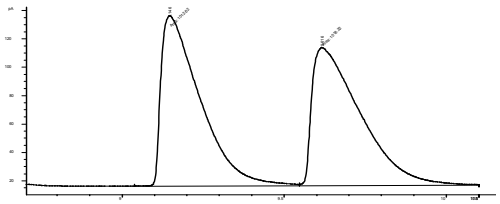
(*R*)-(3-(But-3-enyl)-3-methylcyclopent-1-enyloxy)triethylsilane (3.31). An oven-dried 100 mL round bottom flask was charged with chiral Ag(I)-NHC **Ag-V** (81.0 mg, 0.0750 mmol) and $Cu(OTf)_2$ (54.1 mg, 0.149 mmol), weighed out under a N_2 atmosphere. The round bottom flask was sealed with a septum and wrapped with Teflon® tape before removal from the glove box. Tetrahydrofuran (20.0 mL) was added through a syringe and the resulting solution was allowed to stir for 10 minutes (during this time the solution becomes deep blue) before allowing to cool –78 °C (dry ice/acetone bath). Trimethylaluminum (0.595 mL, 6.00 mmol) (PYROPHORIC, USE EXTREME CAUTION) was added, which resulted in a dark brown solution. After two minutes at –78 °C, 3-(but-3-enyl)cyclopent-2-enone[189] (286 μL, 2.00 mmol) was added to the mixture through a syringe. After 36 h at –78 °C (cryocool), Et_3SiOTf (1.81 mL, 8.00 mmol) was added and the mixture was allowed stir for another 4 h. The reaction was quenched upon addition of a saturated aqueous solution of sodium bicarbonate (20 mL). After allowing the mixture to warm to 22 °C and stir for 15 minutes, the solution was passed through a short plug of celite (10 cm x 20 cm) eluted with Et_2O (100 mL). The filtrate was washed with saturated sodium potassium tartrate (2 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Purification of the clear oil by silica gel column chromatography (1% Et_3N/petroleum ether to 1% Et_3N/2% Et_2O/petroleum ether, gradient) yielded **3.31** (382 mg, 1.43 mmol, 71.5%) as a clear oil. **IR (neat):** 2954 (s), 2913 (m), 2877 (m), 1642 (s), 1457 (w), 1413 (w), 1339 (m), 1246 (s), 1197 (w), 1131

(189) (a) "A Short Synthesis of Tricyclo[4.2.0.$0^{1,4}$]octanes," Wolff, S.; Agosta, W. C. *J. Org. Chem.* **1981**, *46*, 4821-4825. (b) "New Route to Azaspirocycles via the Organolithium-Mediated Conversion of β-Alkoxy into Cyclopentenyl Amines," Moore, S. P.; Coote, S. C.; O'Brien, P. O.; Gilday, J. *Org. Lett.* **2006**, *8*, 5145-5148.

(w), 974 (w), 928 (m), 907 (m), 808 (s), 745 (s), 730 (s) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.83 (1H, dddd, *J* = 16.8, 10.0, 6.4, 6.4 Hz), 4.99 (1H, dq, *J* = 17.2, 1.6 Hz), 4.90 (1H, dddd, *J* = 10.0, 3.6, 1.6, 1.6 Hz), 4.49 (1H, t, *J* = 1.6 Hz), 2.32-2.27 (2H, m), 2.05-1.97 (2H, m), 1.71 (1H, ddd, *J* = 12.4, 8.4, 6.0 Hz), 1.56 (1H, ddd, *J* = 13.2, 9.2, 6.4 Hz), 1.44-1.35 (2H, m), 1.02 (3H, s), 0.97 (9H, t, *J* = 7.6 Hz), 0.68 (6H, q, *J* = 8.0 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 153.5, 140.1, 113.8, 112.1, 45.1, 42.2, 35.2, 33.3, 29.9, 28.1, 6.8, 5.0; **HRMS (ESI+):** Calcd for $C_{16}H_{31}OSi$ (M^++H): 267.21442, Found 267.21421; **Optical Rotation:** $[\alpha]_D^{22}$ +3.16 (*c* 1.03, $CHCl_3$) for an enantiomerically enriched sample of 84% ee.

Enantiomeric purity was determined by chiral GLC analysis in comparison with authentic racemic material of the derived ketone (**3.30**) prepared through hydrolysis of the enol silane (HCl (aq), MeOH). (84% ee shown; chiral dex GTA column, 15 psi, 110 ^{o}C).

(*R*)-3-(but-3-enyl)-3-methylcyclopentanone (3.30): IR (neat): 2962 (m), 2942 (m), 2879 (m), 1746 (s), 1646 (w), 1476 (w), 1413 (w), 1381 (w), 1268 (w), 1167 (w), 997 (w), 909 (w) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.45 (1H, dddd, *J* = 17.0 10.1, 6.4, 6.4 Hz), 4.74 (1H, dd, *J* = 17.0, 1.6 Hz), 4.90 (1H, dd, 10.2, 1.6 Hz), 2.26-2.19 (2H, m), 2.11-1.96 (4H, m), 1.82-1.69 (2H, m), 1.47 (1H, d, *J* = 8.0 Hz) 1.45 (1H, d, *J* = 7.9 Hz), 1.02 (3H, s); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 219.8, 138.8, 114.5, 52.3, 41.0, 39.5, 36.8, 35.3, 29.2, 24.9; **HRMS (ESI+):** Calcd for $C_{10}H_{17}O$ (M^++H): 153.12794, Found 153.12732; **Optical Rotation:** $[\alpha]_D^{22}$ +26.0 (*c* 1.95, $CHCl_3$) for an enantiomerically enriched sample of 84% ee.



#	Time	Area	Height	Width	Area%
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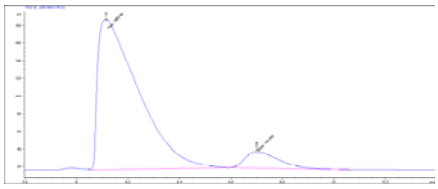
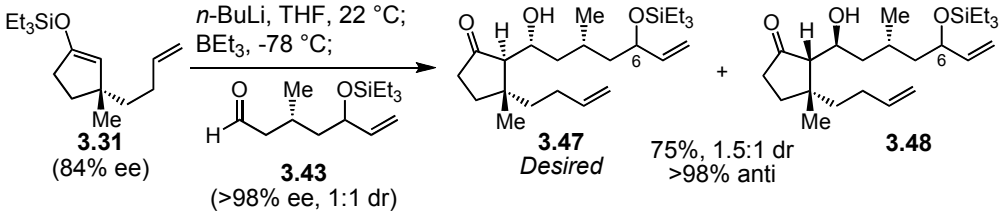
2	9.616	1018.2	97.4	0.1743	50.138

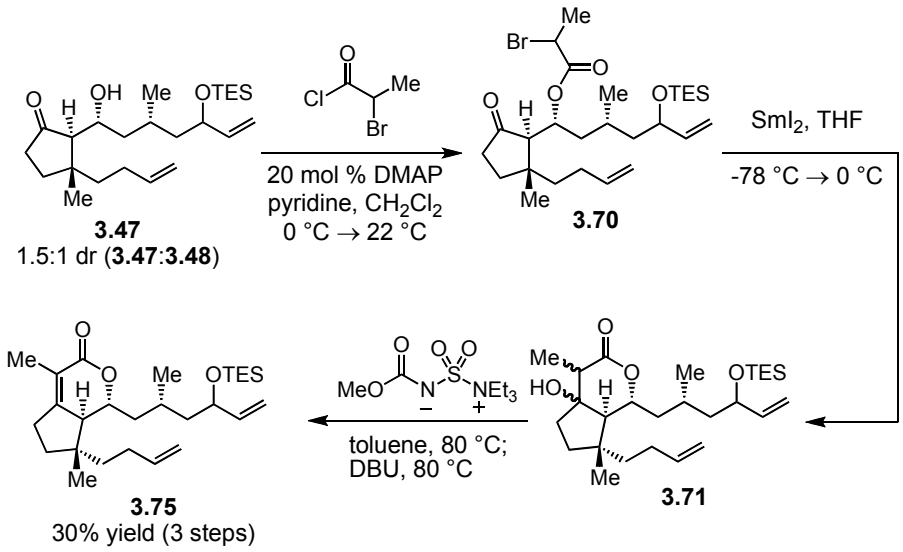


#	Time	Area	Height	Width	Area%
1	9.115	1863	170	0.1826	91.843
2	9.7	165.5	18.4	0.1497	8.157



β-Hydroxy ketones 3.47/3.48. *n*-Butyllithium (940 μL, 1.43 mmol, 1.52 M in hexane) was added to a –78 °C solution of enolsilane **3.31** (382 mg, 1.43 mmol) in THF (11.5 mL). The mixture was allowed to warm to 22 °C and stir for 1 h. At this time, the mixture was allowed to cool to –78 °C and BEt_3 (603 μL, 4.29 mmol) was added. After five minutes, a solution of aldehyde **3.43** (596 mg, 2.30 mmol) in THF (2 mL) was added dropwise over five minutes. After 15 minutes, the reaction was quenched though the addition of a saturated aqueous solution of ammonium chloride (10 mL) and allowed to warm to 22 °C and stir for 2 hours. The resulting solution was washed with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and

concentrated to afford a pale yellow oil. Purification by silica gel column chromatography (5% EtOAc/petroleum ether to 15% EtOAc/petroleum ether, gradient) yielded **3.47/3.48** (437 mg, 1.07 mmol, 74.8%, 1.5:1 mixture) as a clear oil. Further purification by silica gel column chromatography (5% EtOAc/petroleum ether) provided a 4:1 mixture of **3.47** (3:2 dr at C6) and **3.48**, which was used in the ring-closing metathesis reaction. Analyzed as a mixture of 3:2 mixture of C6-(*R*) and C6-(*S*) diastereomers (3:2; the identity of the major isomer has not been established). **IR (neat):** 3490 (br s), 2954 (s), 2935 (s), 2913 (s), 2875 (s), 1727 (s), 1641 (w), 1458 (M), 1412 (m), 1379 (w), 1238 (m), 1069 (s), 1005 (s), 919 (s), 742 (m), 727 (s) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.85-5.72 (2H, m), 5.14-5.08 (1H, m), 5.04-4.93 (3H, m), 4.17-4.12 (1H, m), 3.83-3.76 (1H, m), 3.17 ($1H_{maj}$, d, J = 7.2 Hz), 3.07 ($1H_{min}$, d, J = 7.6 Hz), 2.31-2.15 (3H, m), 2.13-1.99 (3H, m), 1.93-1.90 (1H, m), 1.81-1.36 (9H, m), 1.32-1.22 (1H, m), 0.98 ($3H_{min}$, s), 0.97 ($3H_{maj}$, s), 0.92 (9H, t, J = 8.0 Hz), 0.58 (6H, t, J = 8.0 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 222.1, 221.9, 142.6, 141.5, 138.7, 114.9, 114.5, 113.8, 72.8, 72.2, 67.2, 67.0, 63.5, 63.2, 46.5, 45.3, 44.9, 44.7, 42.5, 42.5, 41.6, 41.5, 46.5, 45.3, 44.9, 44.7, 42.5, 42.5, 41.6, 41.5, 35.1, 36.1, 33.3, 33.3, 28.7, 25.9, 21.2, 20.7, 20.5, 7.1, 5.2, 5.2; **HRMS (ESI+):** Calcd for $C_{24}H_{45}O_3Si$ (M^++H): 409.31380, Found 409.31222; **Optical Rotation:** $[\alpha]_D^{22}$ +39.1 (*c* 0.620, $CHCl_3$).



Lactone 3.75: To a solution of alcohol **3.75** (233 mg, 0.571 mmol), DMAP (14 mg, 0.114 mmol) and pyridine (162 μL, 1.99 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added 2-bromopropionyl bromide (179 μL, 1.71 mmol). The mixture was allowed to warm to 22 °C and stir for 6 h. At this time the reaction was quenched upon addition of pH=7 buffer (5 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was separated, washed with a saturated solution of $CuSO_4$ (5 mL) then H_2O (5 mL), dried over $MgSO_4$, filtered and concentrated to afford a yellow oil. This material was passed through a short plug of silica gel (4 x 1 cm) eluted with 10% EtOAc/petroleum ether to provide **3.70**, which was used in the subsequent transformation without further purification.

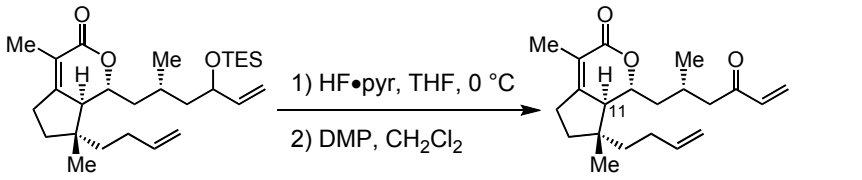
A solution of SmI_2 (0.875 M) in THF was prepared as follows. In a N_2-filled glovebox, Sm(0) (239 mg, 1.59 mmol) and diiodoethane (297 mg, 1.05 mmol) were weighed out into a round bottom flask. The flask was sealed with a septum and removed from the glovebox. Tetrahydrofuran (12 ml) was added through a syringe, and the

mixture was sonicated for two minutes during which time the solution became deep blue. The mixture was allowed to stir for another 15 minutes prior to use. To this solution at -78 °C, was added bromide **3.70** (from previous reaction) dissolved in THF (5 mL) dropwise over 5 minutes. The mixture was allowed to warm to 0 °C and stir for 30 minutes. At this time, the reaction was poured onto ice water (20 mL) and diluted with Et_2O (20 mL). The organic layer was separated and washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated to afford a yellow oil. This material was passed through a short plug of silica gel eluted with 40% EtOAc/petroleum ether to provide **3.71**, which was used in the subsequent transformation without further purification.

To a solution of **3.71** (from previous reaction) in toluene (7 mL) was added Burgess reagent[190] (104 mg, 0.44 mmol). The solution was allowed to warm to 80 °C and stir for 20 min. After allowing the mixture to cool to 22 °C, it was passed through a short plug of silica gel (4 x 1 cm) eluted with EtOAc. The filtrate was concentrated to provide a yellow oil, which was immediately dissolved in toluene (7 mL). Diazabicyclo[5.4.0]undec-7-ene (65.8 μL, 0.44 mmol) was added and the mixture allowed to warm to 80 °C and stir for 12 h. At this time, the mixture was allowed to cool to 22 °C and concentrated to afford a yellow residue. Purification by silica gel column chromatography (2.5% EtOAc/petroleum ether to 10 % EtOAc/petroleum ether, gradient) afforded **3.75** (77.0 mg, 173 μmol, 30.3% yield from **3.47**) as a clear oil. Analyzed as approximately a 1:1:1:1 mixture of diastereomers. **IR (neat):** 2954 (m), 2935 (m), 2875

(190) "The Reactions of an N-Sulfonylamine Inner Salt," Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744–4745.

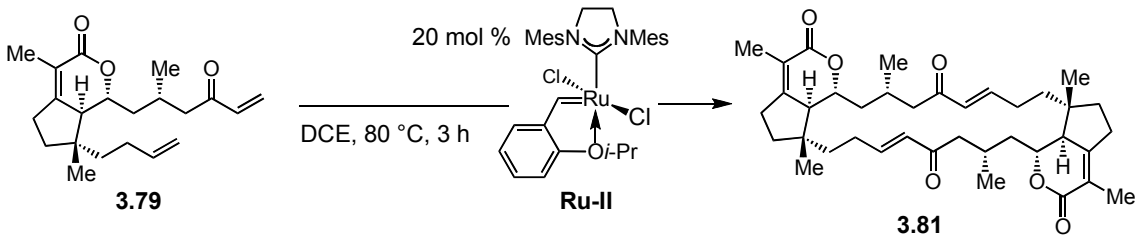
(m), 1712 (s), 1458 (w), 1418 (w, 1379 (w), 1237 (w), 1099 (m), 1004 (m), 990 (m), 915 (m), 742 (m), 669 (m) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.85-5.72 (2H, m), 5.17-5.11 (1H, m), 5.07-4.93 (3H, m), 4.30-4.12 (2H, m), 2.46-2.28 (3H, m), 2.12-1.90 (3H, m), 1.80 (3H, m), 1.70-1.06 (8H, m), 1.00-0.90 (12H, m), 0.82 (3H (one diastereomer), s) 0.82 (3H (one diastereomer), s), 0.62-0.55 (6H, m); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 166.7, 166.7, 166.6, 166.5, 162.0, 161.9, 161.9, 161.7, 142.5, 142.2, 141.1, 138.8, 138.7, 120.3, 120.3, 120.1, 120.1, 115.0, 114.9, 114.9, 114.7, 114.1, 113.9, 79.0, 78.4, 77.3, 72.9, 72.6, 72.3, 72.2, 55.8, 55.7, 53.1, 53.0, 46.9, 46.8, 45.2, 44.8, 44.6, 44.3, 42.2, 42.0, 42.0, 41.7, 41.5, 41.5, 37.7, 36.0, 32.0, 32.0, 29.4, 28.5, 27.8, 27.7, 26.4, 26.4, 25.6, 25.1, 25.1, 21.3, 21.2, 19.5, 19.3, 18.8, 13.0, 13.0, 7.1, 7.1, 5.2, 5.2, 5.1; **HRMS (ESI+):** Calcd for $C_{27}H_{47}O_3Si$ (M^++H): 447.32945, Found 447.32915.



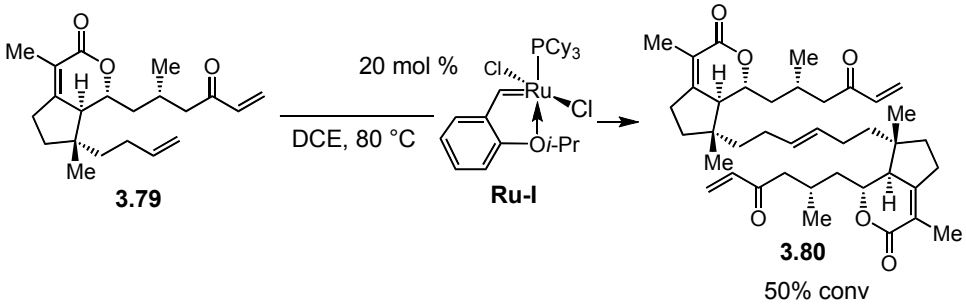
Enone 3.76: To a solution of silylether **3.75** (77.0 mg, 0.172 mmol) dissolved in THF (4.3 mL) at 0 °C was added HF•pyr (~50 μL) dropwise over 5 minutes. The mixture was allowed to stir at 22 °C for 1 h at which time the reaction was quenched upon addition of a saturated solution of aqueous $NaHCO_3$ (5 mL). The mixture was washed with CH_2Cl_2

(2 x 10 mL) and the combined organic layers were dried over $MgSO_4$ filtered and concentrated to afford a yellow oil. The residue was passed through a short plug of silica gel (4 x 1 cm) eluted with 40% EtOAc/petroleum ether to provide to the alcohol, which was used in the subsequent transformation without further purification.

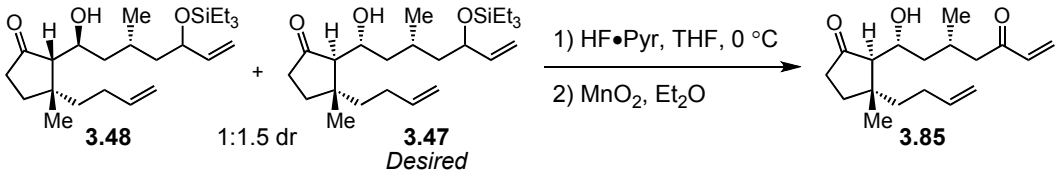
To a solution of the alcohol (from previous reaction) in CH_2Cl_2 (6.2 mL) was added DMP (184 mg, 0.436 mmol) and the mixture allowed to stir for 30 min at 22 °C. At this time, the solution was diluted with Et_2O (20 mL) and passed through a short plug of silica gel (4 x 1 cm) eluted with Et_2O. The filtrate was concentrated to afford a clear oil, which was purified by silica gel column chromatography (10% EtOAc/petroleum ether to 30% EtOAc/petroleum ether, gradient) to provide **3.76** (21.0 mg, 0.0636 mmol, >20:1 dr, 36.9% yield from **3.75**) as a colorless oil. **IR (neat):** 2957 (m), 2923 (m), 2872 (m), 1709 (s), 1677 (m), 1640 (w), 1615 (w), 1456 (w), 1398 (w), 1380 (w), 1305 (w), 1164 (m), 1099 (m), 989 (m), 910 (w) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.34 (1H, dd, *J* = 17.6, 10.4 Hz), 6.24 (1H, dd, *J* = 17.6, 1.2 Hz), 5.87-5.77 (2H, m), 5.04 (1H, dq, *J* = 17.2, 1.6 Hz), 4.97 (1H, dq, *J* = 10.4, 1.2 Hz), 4.24 (1H, ddd, *J* = 12.0, 9.6, 2.8 Hz), 2.82 (1H, dd, *J* = 15.2, 5.2 Hz), 2.53-2.44 (3H, m), 2.40-2.35 (2H, m), 2.19-2.01 (2H, m), 1.82 (3H, dt, *J* = 3.2, 1.6 Hz), 1.80-1.64 (5H, m), 1.46 (1H, ddd, *J* = 18.0, 16.8, 5.2 Hz), 1.01 (3H, d, *J* = 6.8 Hz), 0.85 (3H, s); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 201.0, 166.5, 162.2, 138.8, 137.0, 128.7, 120.2, 114.9, 78.9, 53.0, 45.6, 44.9, 41.3, 40.3, 37.6, 29.4, 27.8, 26.4, 21.2, 19.3, 13.0; **HRMS (ESI+):** Calcd for $C_{21}H_{31}O_3$ (M^++H): 331.22732, Found 331.22791. **Optical Rotation:** $[\alpha]_D^{22}$ -21.0 (*c* 0.726, $CHCl_3$).



22-membered ring 3.81: To a solution of **3.79** (5.0 mg, 0.015 mmol) in 1,2-dichloroethane (15 mL) was added **Ru-II** (1.9 mg, 0.0030 mmol). The mixture was allowed to warm to reflux and stir for 3 h. At this time, the solution was allowed to cool to 22 °C and concentrated under reduced pressure. The green residue was purified by silica gel chromatography (10% EtOAc/petroleum ether to 80% EtOAc/petroleum ether, gradient) to provide **3.81** as a clear oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.80 (2H, dt, *J* = 16.0, 7.2 Hz), 6.09 (2H, d, *J* = 15.6 Hz). 4.28 (2H, dd, *J* = 11.6, 8.0 Hz), 2.60 (2H, dd, *J* = 17.6, 10.4 Hz), 2.46 (4H, br s), 2.37 (2H, dd, *J* = 17.6, 3.2 Hz), 2.31-2.21 (4H, m), 2.20-2.10 (2H, m), 1.83 (6H, t, *J* = 0.8 Hz), 1.73-1.61 (8H, m), 1.46 (2H, dt, *J*= 12.4, 4.8 Hz), 1.35-1.25 (4H, m), 1.15 (6H, d, *J* = 6.8 Hz), 0.97 (6H, s); **HRMS (ESI+):** Calcd for $C_{38}H_{53}O_6$ (M^++H): 605.38421, Found 605.38636.



Cross-Metathesis Dimer 3.80 : To a solution of **3.79** (1.5 mg, 0.0045 mmol) in 1,2-dichloroethane (4.5 mL) was added **Ru-I** (0.55 mg, 0.91 μmol) The mixture was allowed to warm to reflux and stir for 3 h. At this time, the solution was allowed to cool to 22 °C and concentrated under reduced pressure. The green residue was purified by silica gel chromatography (10% EtOAc/petroleum ether to 50% EtOAc/petroleum ether, gradient) to provide **3.80** as a clear oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.35 (2H, dd, *J* = 17.6, 3.6 Hz), 6.24 (2H, ddd, *J* = 17.6, 4.0, 1.2 Hz), 5.83 (2H, d, *J* = 10.4 Hz), 5.40 (2H, dt, *J* = 20.0, 4.0 Hz), 4.23 (2H, t, *J* = 10.8 Hz), 2.86-2.80 (2H, m), 2.77-2.35 (12H, m), 2.97 (6H, br s), 1.82 (6H, s), 1.77-1.40 (8H, m), 1.01 (6H, d, *J* = 6.8 Hz), 0.86 (3H, s), 0.84 (3H, s); **HRMS (ESI+):** Calcd for $C_{40}H_{57}O_6$ (M^++H): 633.41551, Found 633.41390.

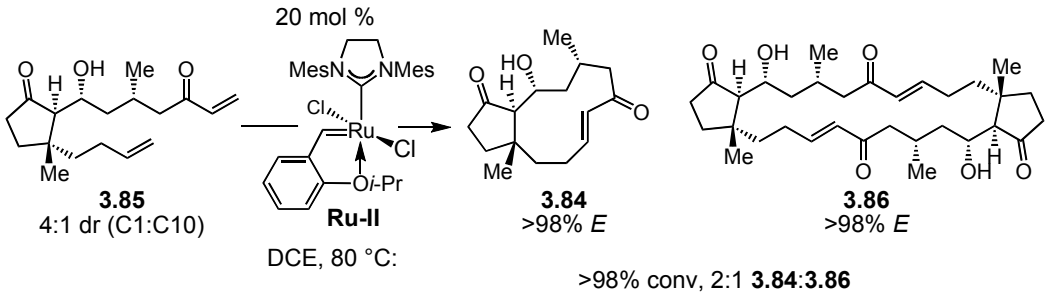


Enone 3.85: To a solution of silyl ethers **3.47/3.48** (209 mg, 0.512 mmol, 1.5:1) in THF (10 mL) at 0 °C was added HF•pyr (~50 μL). After 15 minutes, the reaction was quenched upon addition of a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a yellow oil. This material was passed through a short plug of silica gel (4 x 1 cm) eluted with 40% EtOAc/petroleum ether. The filtrate was

concentrated to provide the alcohol, which was used in the subsequent transformation without further purification.

To a solution of the alcohol (74 mg from previous reaction) in Et_2O (11 mL) was added MnO_2 (~740 mg). The mixture was allowed to stir for 3 h at which time the mixture was passed through a short plug of silica gel (4 x 1 cm) eluted with EtOAc. The filtrate was concentrated to provide a clear oil, which was purified by silica gel column chromatography (10% EtOAc/petroleum ether to 30% EtOAc/petroleum ether, gradient) to afford 25 mg of **3.85** (0.086 mmol, 34% yield from, **3.47/3.48**) as a 4:1 mixture of diastereomers.[191] Major diastereomer: **IR (neat):** 3489 (br s), 2956 (m), 2929 (m), 2873 (w), 1725 (s), 1678 (m), 1640 (w), 1615 (w), 1455 (w), 1404 (m), 1381 (m), 1381 (m), 1143 (m), 1072 (m), 1056 (m), 992 (m), 911 (m) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.35 (1H, dd, *J* = 18.0, 10.4 Hz), 6.24 (1H, dd, *J* = 17.6, 1.2 Hz), 5.88-5.78 (2H, m), 5.05 (1H, dq, *J* = 17.2, 1.6 Hz) 4.98 (1H, dd, *J* = 10.4, 2.0 Hz), 3.83-3.77 (1H, m), 3.49 (1H, d, *J* = 6.0 Hz), 2.76 (1H, dd, *J* = 14.8, 5.2 Hz), 2.39-2.20 (4H, m), 2.14-2.07 (2H, m), 1.99 (1H, d, *J* = 4.4 Hz), 1.78-1.64 (4H, m), 1.53-1.43 (2H, m), 0.99 (3H, s), 0.98 (3H, d, *J* = 6.4 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 222.5, 201.2, 138.7, 137.0, 128.5, 115.0, 67.3, 63.3, 46.2, 43.8, 42.6, 41.5, 36.1, 33.3, 28.8, 26.5, 21.0, 20.4; **HRMS (ESI+):** Calcd for $C_{18}H_{27}O_2$ (M^+-H_2O+H): 275.20110, Found 275.20010.

(191) It seems that under the reaction conditions (MnO_2, Et_2O, 22 °C) the corresponding allylic alcohol or enone of minor diastereomer **3.48** decomposed. Analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture after passage through a short plug of silica gel (100% EtOAc) reveals the mixture is enriched in major diastereomer **3.47** (4:1, **3.47**:**3.48**).

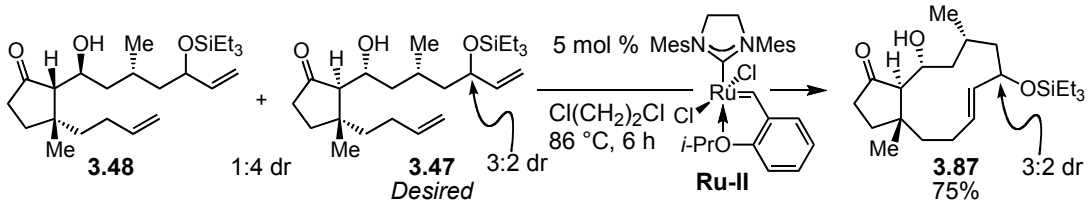


11-membered ring 3.84 and 22-membered ring 3.86: To a solution of **3.85** (11.0 mg, 0.038 mmol) in 1,2-dichloroethane (37 mL) was added **Ru-II** (4.7 mg, 0.0075 mmol). The mixture was allowed to warm to reflux and stir for 1 h. At this time, the solution was allowed to cool to 22 °C and concentrated under reduced pressure. The green residue was purified by silica gel chromatography (20% EtOAc/petroleum ether to 60% EtOAc/petroleum ether, gradient) to provide **3.84** as a white solid and **3.86** as a clear oil.

3.84: m.p. 170-181 °C; **IR (neat):** 3541 (m), 2957 (m), 2920 (m), 2871 (w), 1728 (s), 1665 (s), 1456 (w), 1401 (w), 1379 (w), 1268 (w), 1231 (w), 1211 (w), 1178 (w), 1153 (w), 1036 (m), 1002 (m), 951 (m) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.47 (1H, ddd, *J* = 16.4, 8.8, 5.2 Hz), 6.02 (1H, dd, *J* = 16.4, 0.8 Hz), 3.83 (1H, dd, *J* = 12.0, 8.8 Hz), 3.25 (1H, dd, *J* = 12.0, 6.0 Hz), 2.50-2.43 (1H, m), 2.39-2.20 (5H, m), 2.14-2.10 (2H, m), 1.91-1.79 (4H, m), 1.61-1.55 (1H, m), 1.32-1.25 (1H, m), 1.05 (3H, s), 1.04 (3H, d, *J* = 7.2 Hz); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 219.9, 203.0, 148.4, 134.0, 67.3, 64.5, 47.1, 43.2, 42.7, 39.6, 35.4, 34.1, 30.7, 27.5, 22.6, 22.5; **HRMS (ESI+):** Calcd for $C_{16}H_{25}O_3$ (M^++H): 265.18037, Found 265.18097.

3.86: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (2H, dt, *J* = 15.6, 6.4 Hz), 6.12 (2H, d, *J* = 15.6 Hz), 3.57-3.52 (2H, m), 3.17 (2H, d, *J* = 6.4 Hz), 2.58 (2H, dd, *J* = 17.2, 8.0 Hz),

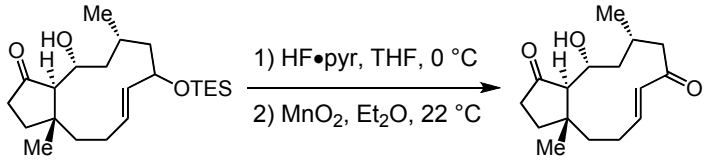
2.46 (2H, dd, J = 17.2, 4.8 Hz), 2.38-2.20 (10H, m), 1.90 (2H, ddd, J = 14.0, 10.8, 4.8 Hz), 1.82 (2H, d, J = 2.4 Hz), 1.79-1.73 (2H, m), 1.68-1.44 (8H, m), 1.09 (6H, d, J = 6.8 Hz), 1.00 (6H, s); **LRMS (ESI+):** Calcd for $C_{32}H_{48}O_6K$ (M^++K): 567.3, Found 567.2. **LRMS (APPI):** Calcd for $C_{32}H_{46}O_5$ (M^+-H_2O+H): 511.3423, Found 511.3504.



Ru-catalyzed ring-closing metathesis product (3.87). To a refluxing solution of Ru-based complex **13** (1.41 mg, 22.5 μmol) in 1,2-dichloroethane (45 mL) under N_2 was added diene **3.47**/**3.48** (18.4 mg, 445 μmol, 4:1 dr, 3:2 at C6 for **3.47**)[192] as a solution in 1,2-dichloroethane (1.0 mL) over 3 h with a syringe pump. Once the addition was complete, the solution was allowed to reflux for an additional 3 h. The mixture was passed through a short plug of silica gel eluted with 30% EtOAc/petroleum ether. The filtrate was concentrated in vacuo and the green oily residue was purified by silica gel column chromatography (2.5% EtOAc/47.5% CH_2Cl_2/50% petroleum ether (to elute **Ru-II**) directly to 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether, gradient) to afford macrocycle **3.87** (10.2 mg, 268 μmol, 75.2%, based of a maximum yield of 80%) as a clear oil. Analyzed as a 3:2 mixture of C6-(*R*) and C6-(*S*) diastereomers (the identity

(192) To obtain pure **3.87**, it is necessary to carry out the RCM with a sample of **3.47:3.48** that contains ≤20% of **3.48**. Catalytic RCM with a sample that is a 1:1 mixture of **3.47**:**3.48**, under otherwise identical conditions, resulted in a complex mixture of products, and attempted isolation of pure **3.87** was not successful.

of the major diastereomer has not been established). **IR (neat):** 3549 (br w), 2951 (s), 2912 (s), 2874 (s), 1727 (s), 1457 (m), 1410 (w), 1380 (w), 1235 (m), 1139 (w), 1062 (s), 1004 (s), 983 (s), 890 (w), 838 (w), 813 (w), 786 (w), 741 (s), 726 (s), 485 (w) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 5.50-5.30 (2H, m), 4.13-4.04 (1H, m), 3.79 ($1H_{min}$, br t, J = 10.8 Hz), 3.58 ($1H_{maj}$, ddd, J = 11.2, 7.2, 3.2 Hz), 2.38 ($1H_{maj}$, s), 2.30-2.03 (5H, m), 1.92-1.47 (7H, m), 1.06-1.01 (4H, m), 0.98 ($3H_{maj}$, s), 0.92 (9H, t, J = 8.0 Hz), 0.59-0.52 (6H, m); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 221.8, 220.8, 137.7, 135.8, 131.3, 129.8, 74.3, 70.9, 69.5, 67.4, 64.0, 62.2, 48.0, 46.3, 45.4, 42.8, 42.7, 41.7, 37.6, 36.5, 35.6, 33.1, 30.3, 29.9, 27.0, 27.0, 25.6, 23.8, 22.7, 7.1, 7.0, 5.1; **HRMS (ESI+):** Calcd for $C_{22}H_{40}O_3SiNa$ (M^++Na): 403.2644, Found 403.2653; **Optical Rotation:** $[\alpha]_D^{22}$ +84.8 (*c* 0.800, $CHCl_3$).

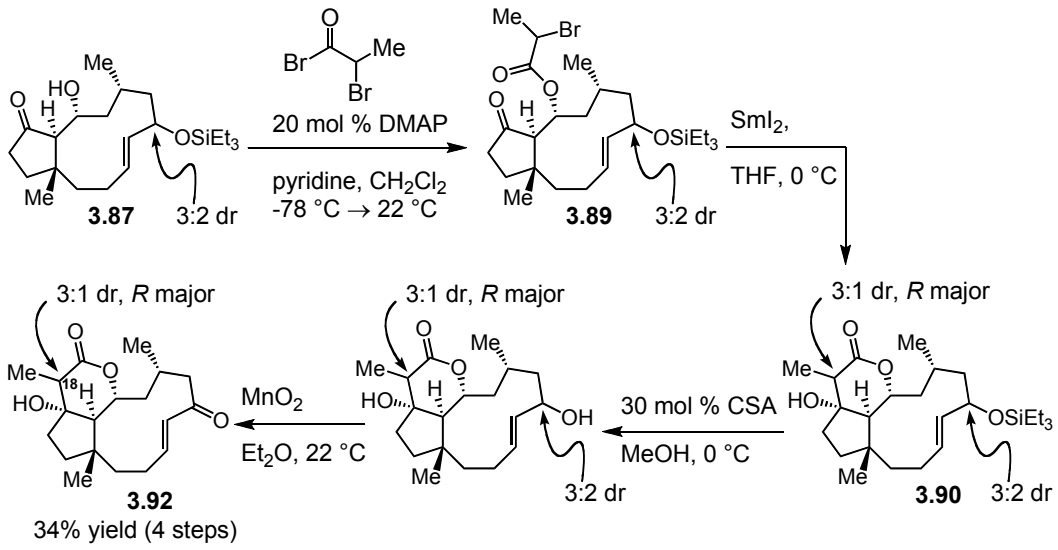


3.87 **3.84** 67% yield

Enone 3.85: To a solution of silyl ether **3.87** (28.6 mg, 0.0753 mmol) in THF (2 mL) at 0 °C was added HF•pyr (~15 μL). After 30 minutes, the reaction was quenched upon addition of a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a yellow oil. This material was passed through a short plug of silica gel eluted with 50% EtOAc/petroleum ether to 100% EtOAc. The filtrate was concentrated to

provide the alcohol, which was used in the subsequent transformation without further purification.

To a solution the alcohol (from previous reaction) in Et_2O (5 mL) was added MnO_2 (~170 mg). The mixture was allowed to stir for 3 h at which time the mixture was passed through a short plug of silica gel eluted with 100% EtOAc. The filtrate was concentrated to provide a white solid, which was purified by silica gel column chromatography (10% EtOAc/petroleum ether to 50% EtOAc/petroleum ether, gradient) to afford 13.4 mg of **3.84** (0.0507 mmol, 67.4% yield from **3.87**) as a white solid. For full characterization see above.



Enone 3.92: To a vial (2 x 7 cm) charged with DMAP (6.12 mg, 50.2 μmol) was added CH_2Cl_2 (500 μL) and pyridine (121 μL, 1.50 mmol). In a separate vial containing

alcohol **3.87** (48.5 mg, 0.125 mmol) and CH_2Cl_2 (2.4 mL) was added 250 μL of the above CH_2Cl_2 solution of DMAP and pyridine. The vial was allowed to cool to –78 °C and 2-bromopropionyl bromide (39.3 μL, 0.375 mmol) was added. The resulting yellow solution was allowed to warm to 22 °C. Upon warming, the mixture becomes heterogeneous then homogenous after several minutes. After 30 min, the remainder of the CH_2Cl_2 solution (250 μL) of DMAP and pyridine followed by 2-bromopropionyl bromide (39.3 μL, 0.375 mmol) were added. The mixture was allowed to stir for another 30 min before the reaction was quenched with pH = 7 buffer (1 mL). The mixture was diluted with Et_2O and the aqueous layer removed. The organic layer was washed successively with a saturated aqueous solution of $CuSO_4$ (5 mL), water (5 mL) and a saturated aqueous solution of sodium bicarbonate (2 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to afford an orange oil. This material was passed through a short plug of silica gel (4 x 1 cm) eluted with 5% EtOAc/petroleum ether to afford **3.89** (~44 mg) as a clear oil. This material was used directly in the subsequent reaction without further purification.

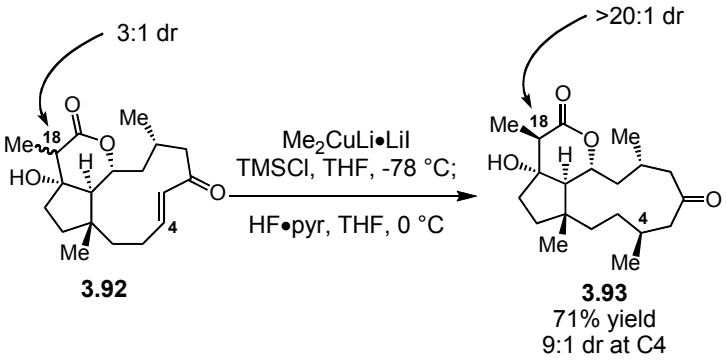
A solution of SmI_2 (0.1 M) in THF was prepared as follows. In a N_2-filled glovebox, Sm(0) (225 mg, 1.50 mmol) and diiodoethane (281 mg, 1.00 mmol) were weighed out into a round bottom flask. The flask was sealed with a septum and removed from the glovebox. Tetrahydrofuran (10 ml) was added through a syringe, and the mixture was sonicated for two minutes during which time the solution became deep blue. The mixture was allowed to stir for another 15 minutes prior to use.

Samarium diiodide (0.1 M in THF) was added dropwise to a solution of bromide **3.89** (~44 mg, from previous reaction) dissolved in THF at 0 °C. The rate of addition was such that with each drop of SmI_2 the solution is allowed to turn from blue to yellow before the next drop is added. Approximately 1.9 mL (2.2 equiv) of the SmI_2 solution was added before the solution remains blue/green for at least 5 minutes. Once the addition was complete, the reaction was quenched through the addition of a saturated aqueous solution of NH_4Cl (5 mL) and diluted with EtOAc (10 mL). The organic layer was separated and the aqueous layers washed with EtOAc (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a pale yellow oil. This material was passed through a short plug of silica gel (4 x 1 cm) eluted with 5% EtOAc/petroleum ether to 30% EtOAc/petroleum ether to afford **3.90** (~27 mg) as a clear oil. This material was used in the subsequent transformation without purification. For a representative ^1H NMR spectrum of this intermediate see below.

To a solution of the silyl ether **3.90** (~27 mg, from previous reaction) in MeOH (1.5 mL) at 0 °C was added (+)-camphorsulfonic acid ((+)-CSA) (~4 mg). After 15 minutes, the reaction was quenched through the addition of a saturated aqueous solution of $NaHCO_3$ (2 mL) and diluted with EtOAc (2 mL). The organic layer was separated and washed with EtOAc (2 x 2 mL). The combined organic layers were then passed through a short plug of silica gel eluted with EtOAc. The filtrate was concentrated and to afford the desired product, which was used in the next transformation without purification.

Manganese dioxide (~500 mg) was added to a solution of the alcohol (from previous reaction) in Et_2O (10 mL). The suspension was allowed to stir for 1 h before

being passed through a short plug of silica gel (4 x 1 cm) eluted with CH_2Cl_2 then EtOAc. The filtrate was concentrated to afford a colorless oil, which was purified by silica gel column chromatography (20% EtOAc/petroleum ether to EtOAc, gradient) to provide the enone **3.92** (14.0 mg, 0.044 mmol, 35.2% yield over 4 steps from **3.87**) as a white foam. Analyzed as a 3:1 mixture of C18-(R) and C18-(S) diastereomers. X-ray quality crystals were obtained by recrystallization from CH_2Cl_2/pentane. **IR (neat):** 3440 (br s), 2936 (m), 1733 (s), 1686 (m), 1655 (s), 1456 (m), 1392 (w), 1322 (w), 1256 (w), 1200 (w), 1108 (w), 1079 (w), 1039 (w), 993 (w), 971 (w) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.66 ($1H_{min}$, ddd, *J* = 16.0, 9.2, 7.2 Hz), 6.51 ($1H_{maj}$, ddd, *J* = 16.0, 10.0, 5.2 Hz), 6.28 ($1H_{maj}$, dd, *J* = 15.6, 0.8 Hz), 6.11 ($1H_{min}$, d, *J* = 16.4 Hz), 4.63 ($1H_{maj}$, 1H, d, *J* = 10.0 Hz), 4.40 ($1H_{min}$, dd, *J* = 9.6, 7.2 Hz), 3.05-3.00 ($1H_{min}$, m), 2.89-2.84 (2H, m), 2.46-2.30 (4H, m), 2.25-2.20 (2H, m), 2.04-1.69 (6H, m), 1.57-1.38 (3H, m), 1.27 ($3H_{min}$, d, *J* = 6.8 Hz), 1.24 ($3H_{maj}$, d, *J* = 6.8 Hz), 1.11-1.08 (3H, m), 0.99 (3H, s); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 202.6, 201.9, 173.7, 173.3, 150.6, 146.4, 135.3, 134.3, 85.1, 84.1, 77.9, 76.7, 62.8, 61.6, 46.3, 46.1, 45.6, 45.2, 45.0, 44.8, 44.7, 44.4, 43.5, 43.2, 41.5, 41.3, 36.2, 35.4, 31.4, 29.8, 29.7, 28.4, 24.1, 22.6, 19.7, 18.2, 9.6, 8.5; **HRMS (ESI+):** Calcd for $C_{19}H_{29}O_4$ (M^++H): 321.20658, Found 321.20547. **Optical Rotation:** $[\alpha]_D^{22}$ +14.1 (*c* 0.313, $CHCl_3$).

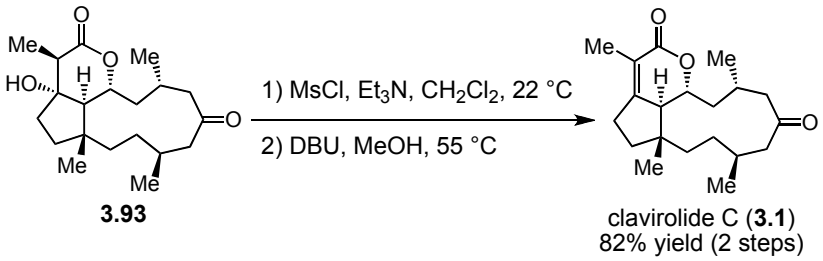


3.92

3.93
71% yield
9:1 dr at C4

Conjugate addition adduct 3.93: To a suspension of CuI (9.52 mg, 50.0 μmol) in THF (1.0 mL) at –78 °C was added MeLi (57.0 μL, 1.74 M in Et_2O, 0.100 mmol). After five minutes the mixture was allowed to warm to 0 °C and stir for five additional minutes. During this time the mixture becomes colorless and homogeneous. The solution was allowed to recool to –78 °C and TMSCl (6.30 μL, 50.0 μmol) followed by enone **3.92** (4.00 mg, 0.0125 mmol) dissolved in THF (1.0 mL) were added. After 15 minutes, the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (2 mL) and H_2O (2 mL). The mixture was allowed to stir until blue (~5 minutes), then washed with EtOAc (3 x 5 mL). The combined organic layers were passed through a short plug of silica gel (4 x 1 cm) eluted with EtOAc. The filtrate was concentrated in vacuo to afford the enol silane, which was immediately dissolved in THF (1 mL) and allowed to cool to 0 °C. To this solution was added HF•pyr (5 drops). After 5 minutes, the mixture was diluted with H_2O (1 mL) and washed with EtOAc (3 x 5 mL). The combined organic layers were passed through a short plug of silica gel (4 x 1 cm) eluted with EtOAc and the filtrate was concentrated to afford a clear oil. Purification by silica gel

chromatography (30% Et_2O/petroleum ether to 100% Et_2O, gradient) to provided **3.93** (3.0 mg, 8.92 μmol, 71% yield) as a white foam. X-ray quality crystals were obtained by recrystallization from CH_2Cl_2/pentane. **IR (neat):** 3460 (br m), 2955 (s), 2926 (s), 2870 (s), 1717 (s), 1457 (m), 1377 (m), 1317 (m), 1200 (m), 1155 (m), 1123 (m), 1109 (w), 1072 (w), 1041 (w) 969 (w), 940 (w) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.22 (1H, t, *J* = 5.2 Hz), 2.86 (1H, q, *J* = 6.8 Hz), 2.61-2.40 (4H, m), 2.32-2.09 (2H, m), 2.01-1.78 (4H, m), 1.75-1.46 (4H, m), 1.38-1.13 (7H, m), 1.04 (3H, d, *J* = 6.4 Hz), 1.02 (3H, d, *J* = 6.8 Hz), 0.84 (3H, s); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 211.2, 173.4, 84.9, 77.8, 60.1, 58.9, 52.9, 51.2, 47.6, 46.2, 45.8, 38.8, 31.3, 30.2, 29.5, 28.9, 24.5, 22.1, 21.3, 9.4; **HRMS (ESI+):** Calcd for $C_{20}H_{33}O_4$ (M^++H): 337.23788, Found 337.23853; **Optical Rotation:** $[\alpha]_D^{22}$ +16.6 (*c* 0.273, $CHCl_3$).



Clavirolide C: To a solution of tertiary alcohol (**3.93**) (2.2 mg, 0.0065 mmol) and Et_3N (9.1 μL, 0.065 mmol) in CH_2Cl_2 cooled to 0 °C was added MsCl (2.7 μL, 0.033 mmol). The mixture was allowed to warm to 22 °C and stir for 15 min at which time additional Et_3N (9.1 μL, 0.065 mmol) and MsCl (2.7 μL, 0.033 mmol) were sequentially added.

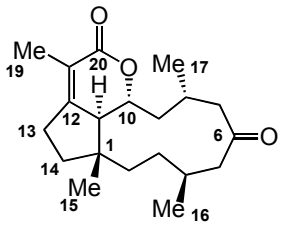
After 15 min, the reaction was quenched upon addition of a saturated aqueous solution of $NaHCO_3$ (1 mL). The combined organic layers were passed through a short plug of silica gel (4 x 1 cm) eluted with EtOAc. The filtrate was concentrated and passed again through a short plug of silica gel (4 x 1 cm) eluted with 30% EtOAc/petroleum ether. The filtrate was concentrated and the residue carried on the in next transformation without purification.

To a solution of the above olefin in MeOH (500 μL) was added DBU (4.9 μl, 0.033 mmol). The solution was allowed to warm to 55 °C and stir for 2 h. At this time, the mixture was passed through a short plug of silica gel (4 x 1 cm) eluted with EtOAc. The filtrate was concentrated and the residue purified by silica gel column chromatography (2.5% EtOAc/pentane to 10% EtOAc/pentane, gradient) to provide clavirolide C (**3.1**) (1.7 mg, 82% yield) as a clear oil. Final ^{1}H NMR spectrum contains 1-5% *eqi*-C4 clavirolide C (inseparable). **IR (neat):** 2955 (m), 2925 (m), 2870 (m), 1703 (s), 1459 (w), 1381 (w), 1336 (w), 1304 (w), 1291 (w), 1260 (w), 1116 (m), 1022 (m), 995 (w), 801 (m), 766 (w), 678 (w) cm $^{-1}$; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 4.17 (1H, ddd, *J* = 11.2, 8.8, 1.2 Hz), 2.70 (1H, dd, *J* = 15.2, 11.6 Hz), 2.53-2.31 (5H, m), 2.18-1.99 (3H, m), 1.91 (1H, dd, *J* = 14.8, 8.4 Hz), 1.81 (3H, ddd, *J* = 2.8, 1.6, 1.6 Hz), 1.76-1.61 (3H, m), 1.52-1.42 (4H, m), 1.14 (3H, d, *J* = 6.4 Hz), 0.96 (3H, d, *J* = 7.2 Hz), 0.87 (3H, s); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 212.0, 166.4, 160.7, 120.1, 78.2, 53.7, 53.7, 52.7 (br), 46.5, 45.0, 43.3, 37.7, 32.7 (br), 29.4, 27.3, 27.0, 22.6, 21.9, 20.1, 12.6; **HRMS (ESI+):** Calcd for $C_{20}H_{31}O_3$ (M^++H): 319.22732, Found 319.22629; **Optical Rotation:** $[\alpha]_D^{22}$ –15.9 (*c* 0.113, $CHCl_3$).

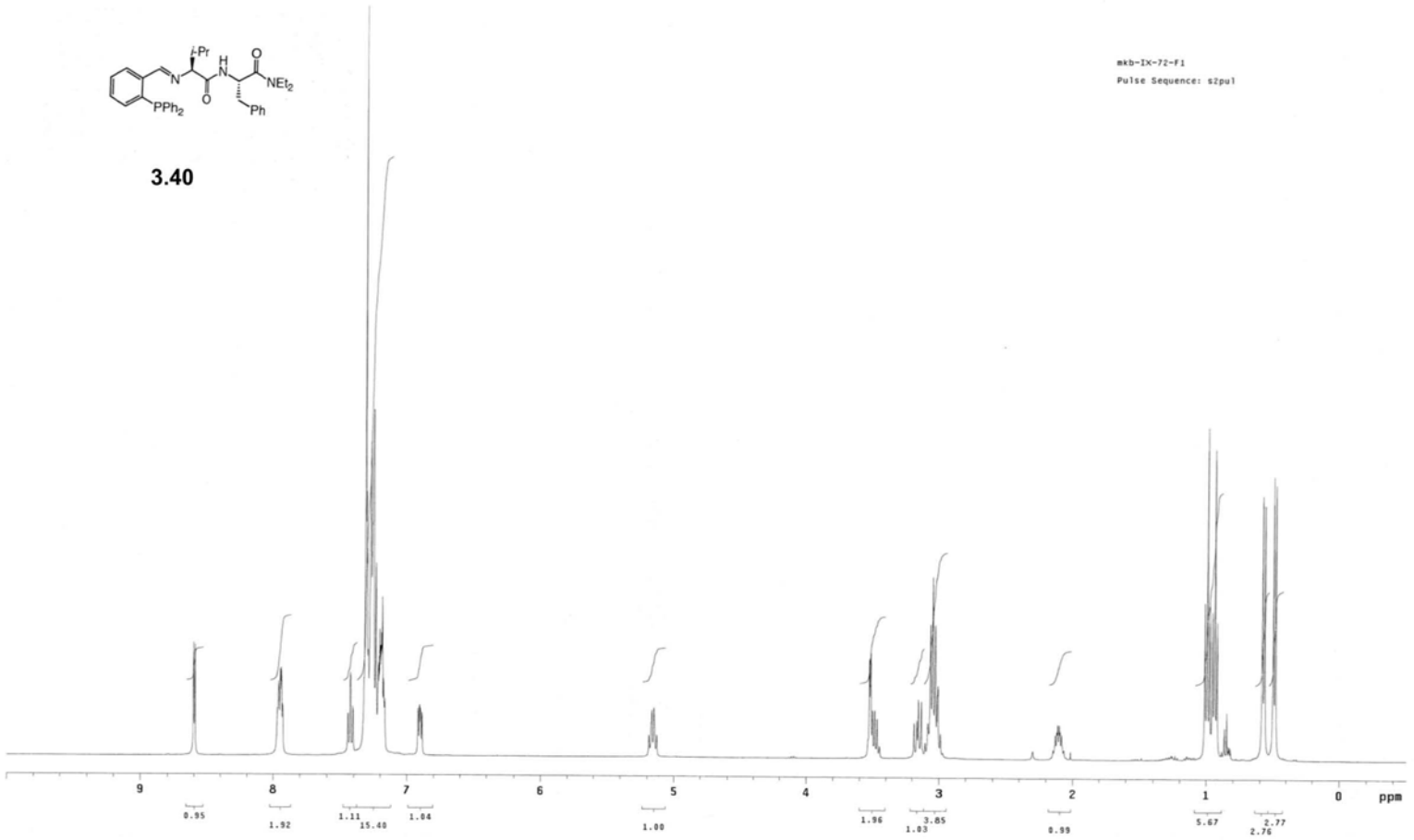
ν Note regarding the optical rotation of clavirolide C: The reported specific rotation value for clavirolide C is $[\alpha]_D^{20}$ –38.5 (c 0.018, MeOH).[193] We obtained a specific rotation of $[\alpha]_D^{22}$ 0.00 (*c* 0.017, MeOH) as well as $[\alpha]_D^{22}$ 0.00 (*c* 0.113, MeOH). It is likely that due to the extremely low concentration (0.018 g/dL) of the sample and the possible low solubility of clavirolide C in MeOH, the original specific rotation value is incorrect. We were able to obtain a reproducible specific rotation in $CHCl_3$: $[\alpha]_D^{22}$ –15.9 (*c* 0.113, $CHCl_3$).

ν Note regarding the ^{1}H NMR spectrum of clavirolide C: A complete ^{1}H NMR spectrum of clavirolide C was not provided in the isolation publication,[193] nor were we able to secure an authentic sample for comparison in spite of repeated attempts to contact authors of the isolation manuscript. Only partial ^{1}H NMR data was provided; as illustrated below, all the reported data closely match the chemical shifts observed for synthetic clavirolide C.

(193) "Four Novel Diterpenoids: Clavirolides B, C, D, and E from the Chinese Soft Coral *Clavularia Viridis*," Su, J.; Zhong, Y.; Zeng, L. *J. Nat. Prod.* **1991**, *54*, 380-385.



	natural clavirolide C ***($CDCl_3$, 90 MHz)***	***synthetic claviroldie C*** ***($CDCl_3$, 400 MHz)***
H-10	4.17, 1H, t, *J* = 10.8 Hz	4.17, 1H, ddd, *J* = 11.2, 8.8, 1.2
H-15	0.87, 3H, s	0.87, 3H, s
H-16	0.95, 3H, d, *J* = 7.3 Hz	0.96, 3H, d, *J* = 7.2 Hz
H-17	1.14, 3H, d, *J* = 6.8 Hz	1.14, 3H, d, *J* = 6.4 Hz
H-19	1.81, 3H, dd, *J* = 3.8, 2.0 Hz	1.81, 3H, ddd, *J* = 2.8, 1.6, 1.6
	($CDCl_3$, 22.5 MHz)	***($CDCl_3$, 125 MHz)***
C-1	44.8	45.0
C-2	46.2	46.5
C-3	32.4	32.7
C-4	26.8	27.0
C-5	53.4	53.7
C-6	211.6	212.0
C-7	53.4	53.7
C-8	29.1	29.4
C-9	43.1	43.3
C-10	77.9	78.2
C-11	52.5	52.7
C-12	160.5	160.7
C-13	27.1	27.3
C-14	37.4	37.7
C-15	22.4	22.6
C-16	21.3	21.9
C-17	19.9	20.1
C-18	119.7	120.1
C-19	12.3	12.6
C-20	165.8	166.4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8
7
6
5
4
3
2
1
0
ppm
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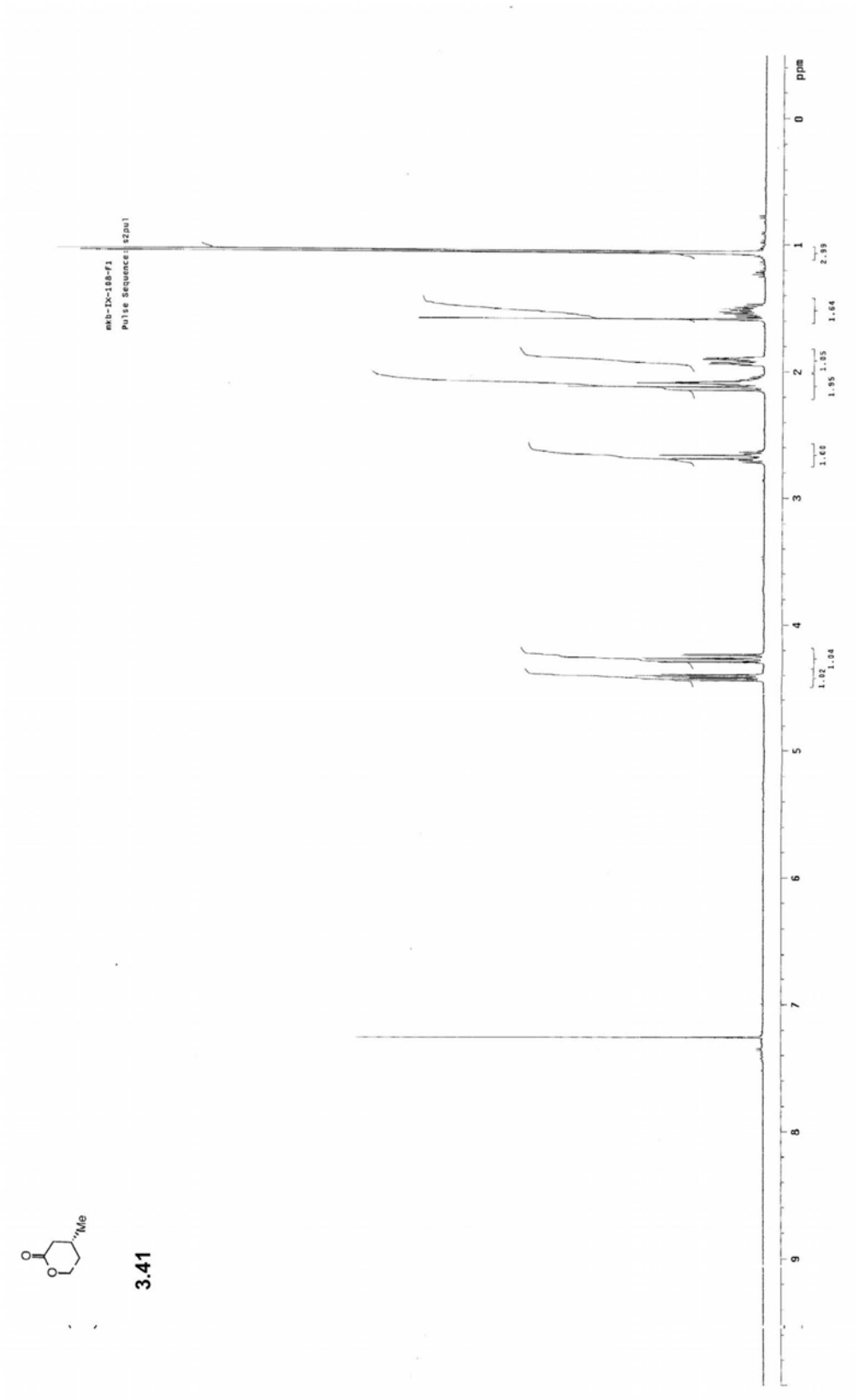
1.92
1.11
15.40
1.04
1.00
1.96
3.85
1.03
0.99
5.67
2.77
2.76

3.40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2
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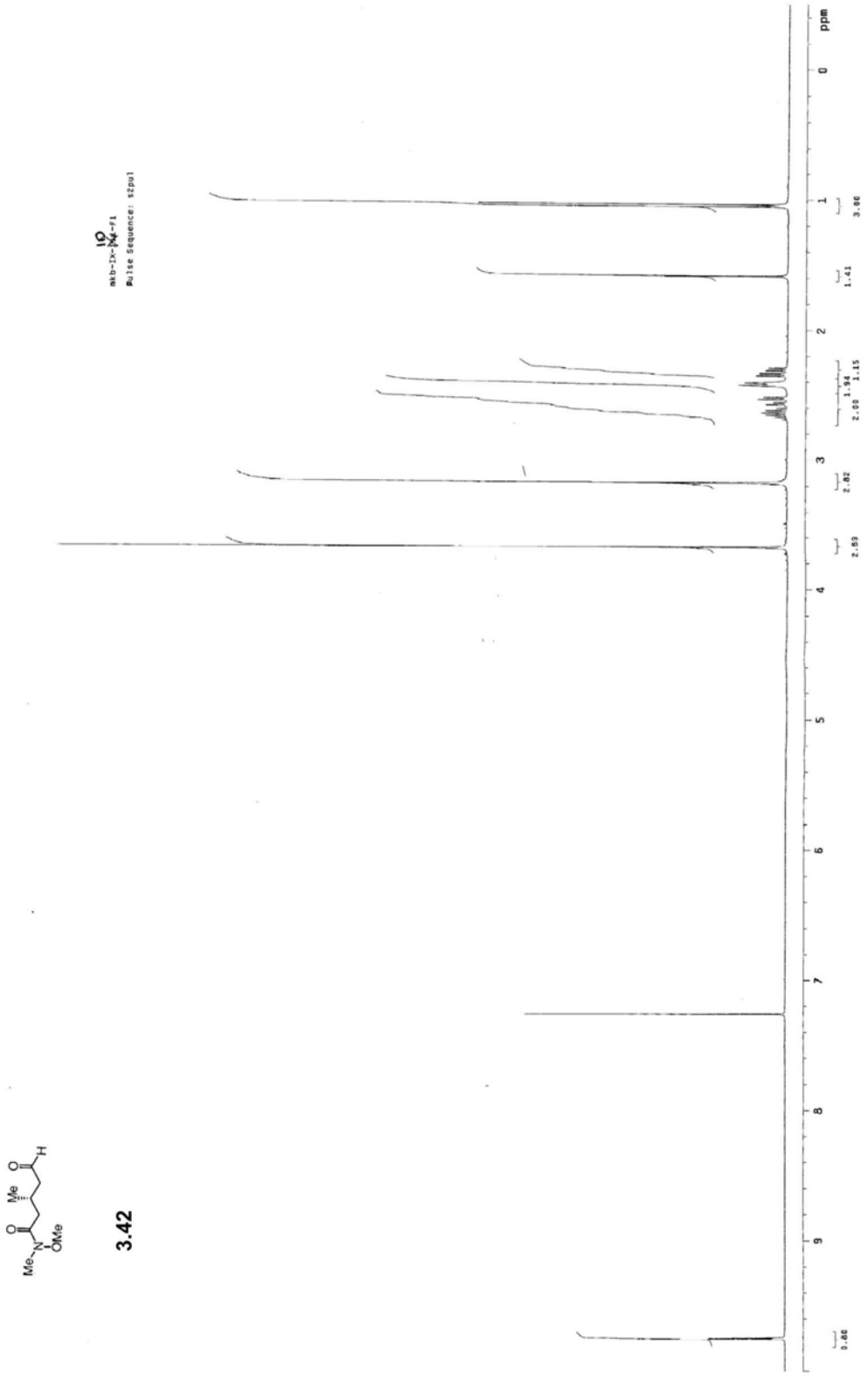
1.95
1.95
1.66
1.02
1.04
Me
O
O

3.41


Me
O
H
O
Me
N
OMe
3.42
19
Pulse Sequence: s2pul
ppm
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1
2
3
4
5
6
7
8
9
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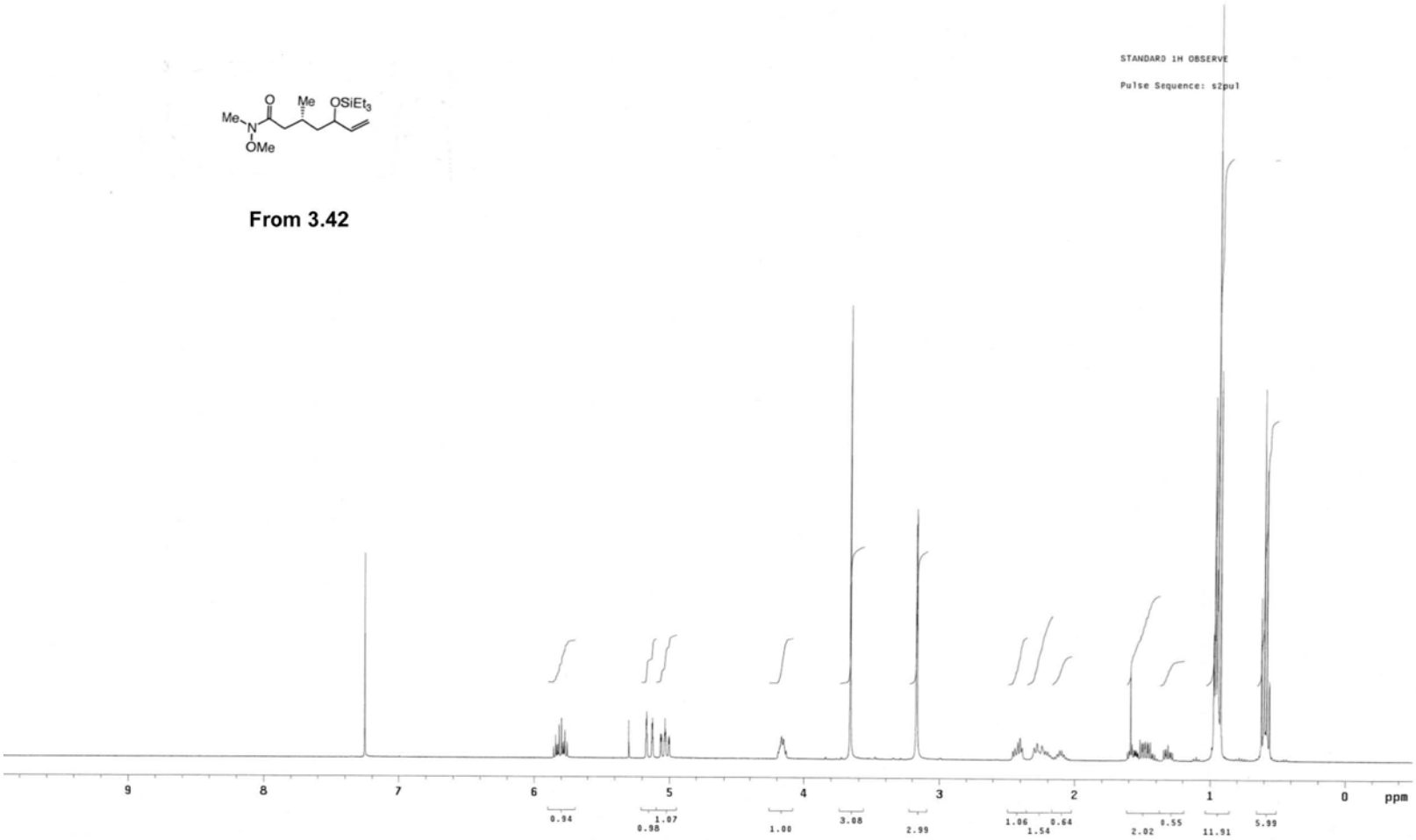
1.41
1.94
1.15
2.00
2.82
2.69
0.86


Me
O
Me
OSiEt3
N
OMe
From 3.42
STANDARD 1H OBSERVE
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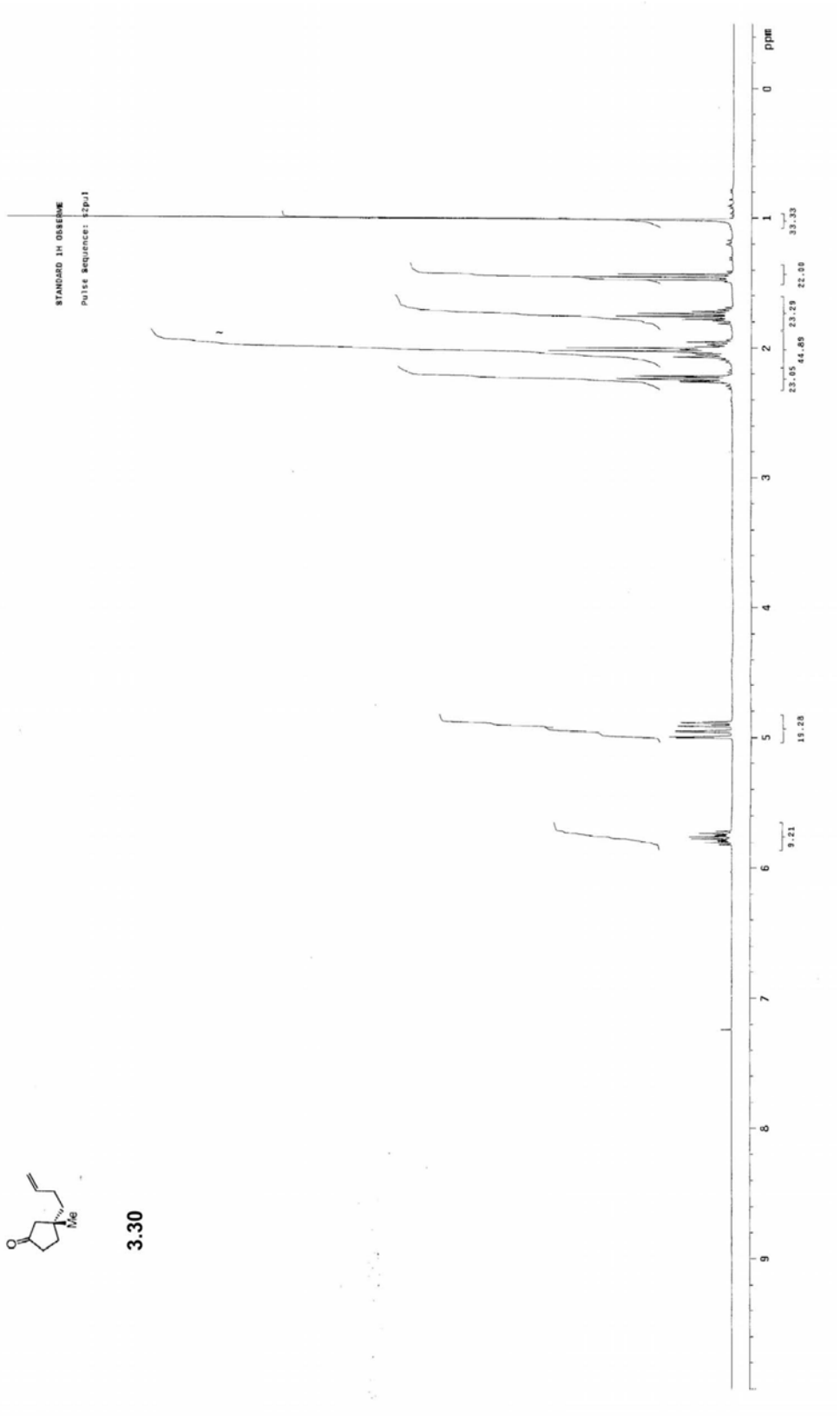
9
8
7
6
5
4
3
2
1
0
ppm
0.94
1.07
0.98
1.00
3.08
2.99
1.06
0.64
1.54
2.02
0.55
11.91
5.99

mkb-IX-77-f1
Pulse Sequence: s2pul
OSiEt3
Me
O
H
3.43
ppm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2
3
4
5
6
7
8
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22.00
23.29
44.89
23.05
15.28
9.21
Me
O

3.30

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ppm
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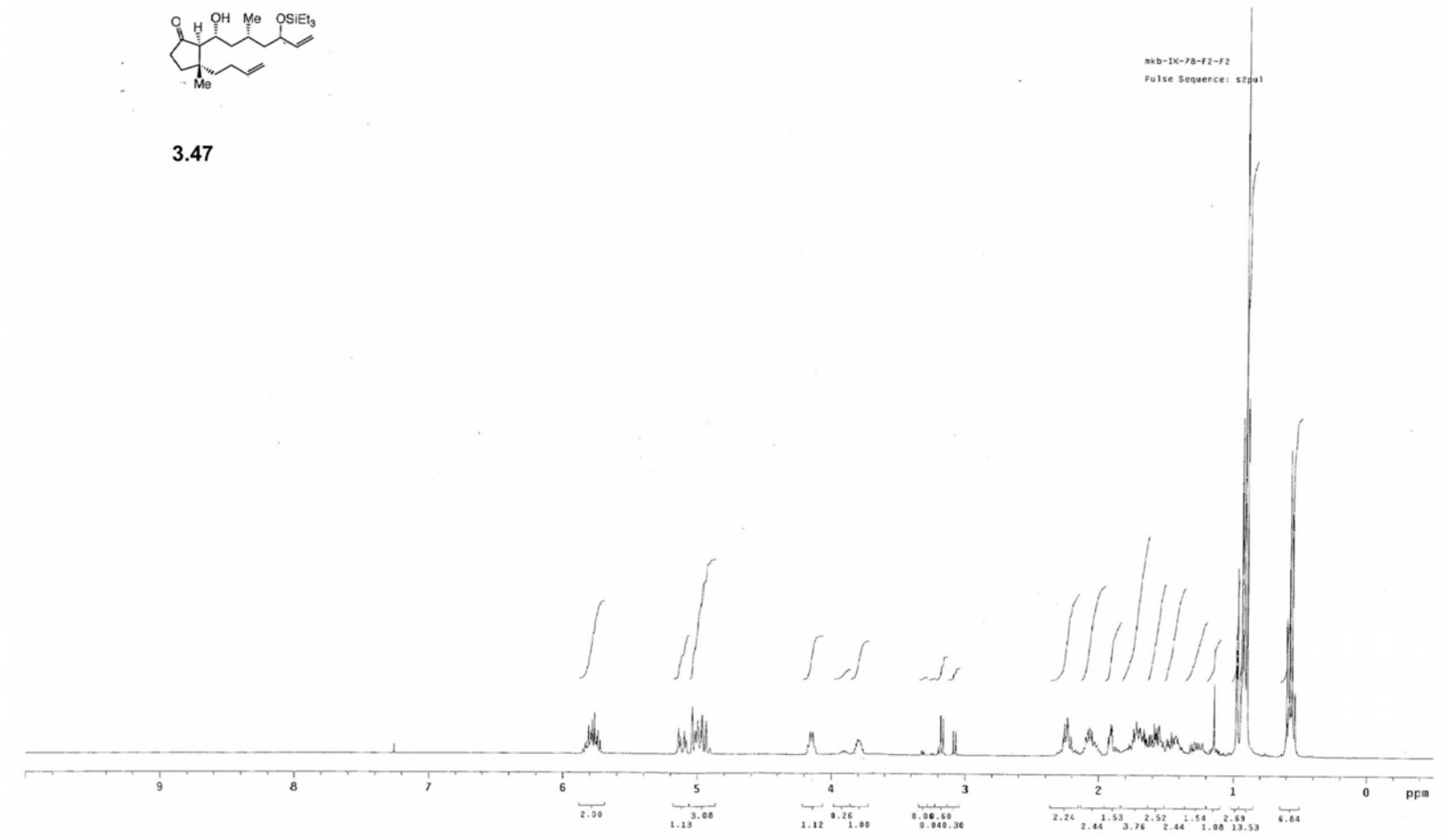
Me
3.31


O
H
OH
Me
OSiEt3
Me
3.47
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8
7
6
5
4
3
2
1
0
ppm
2.00
3.08
1.13
1.12
0.26
1.00
0.06.60
0.040.30
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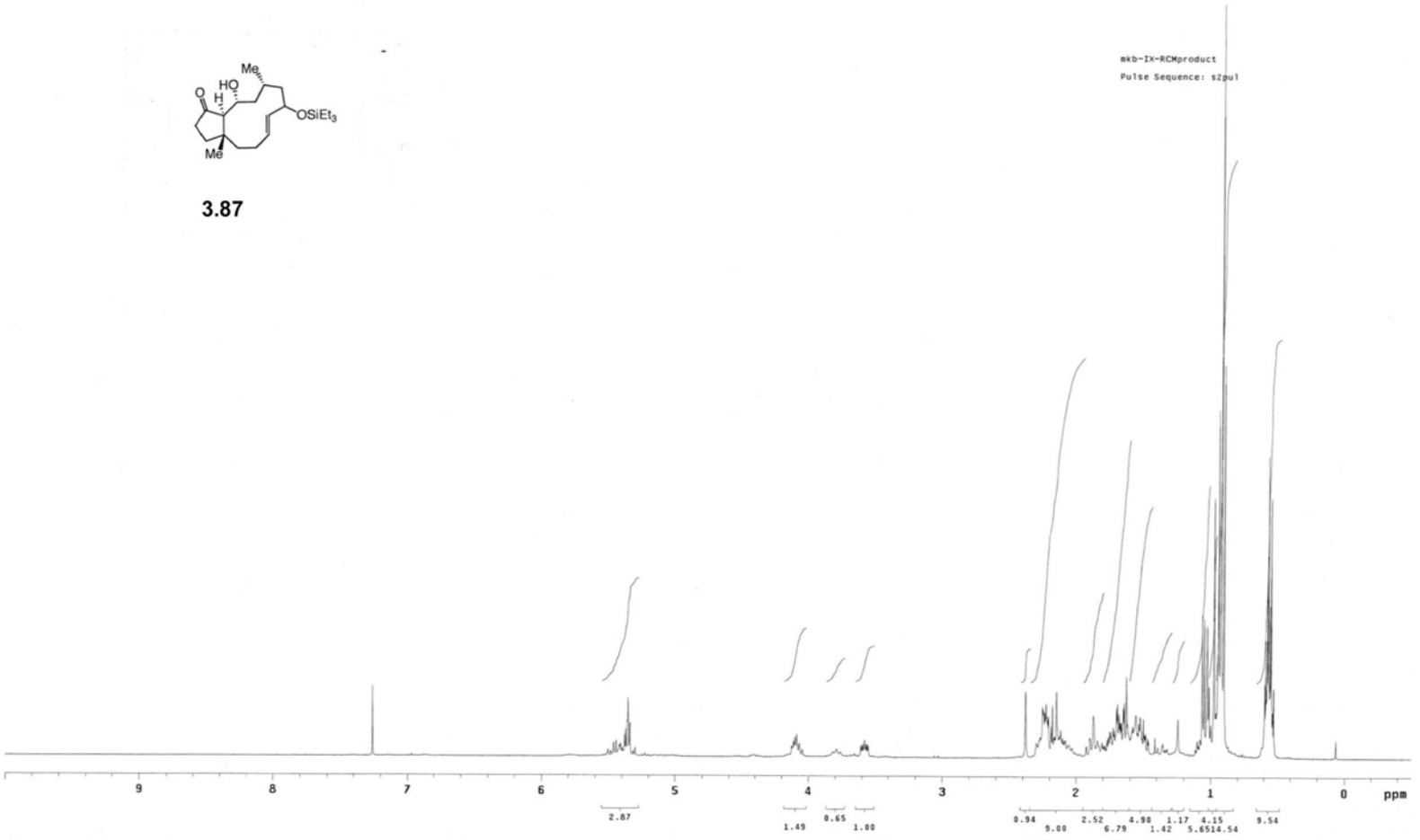
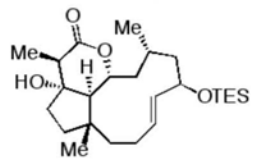
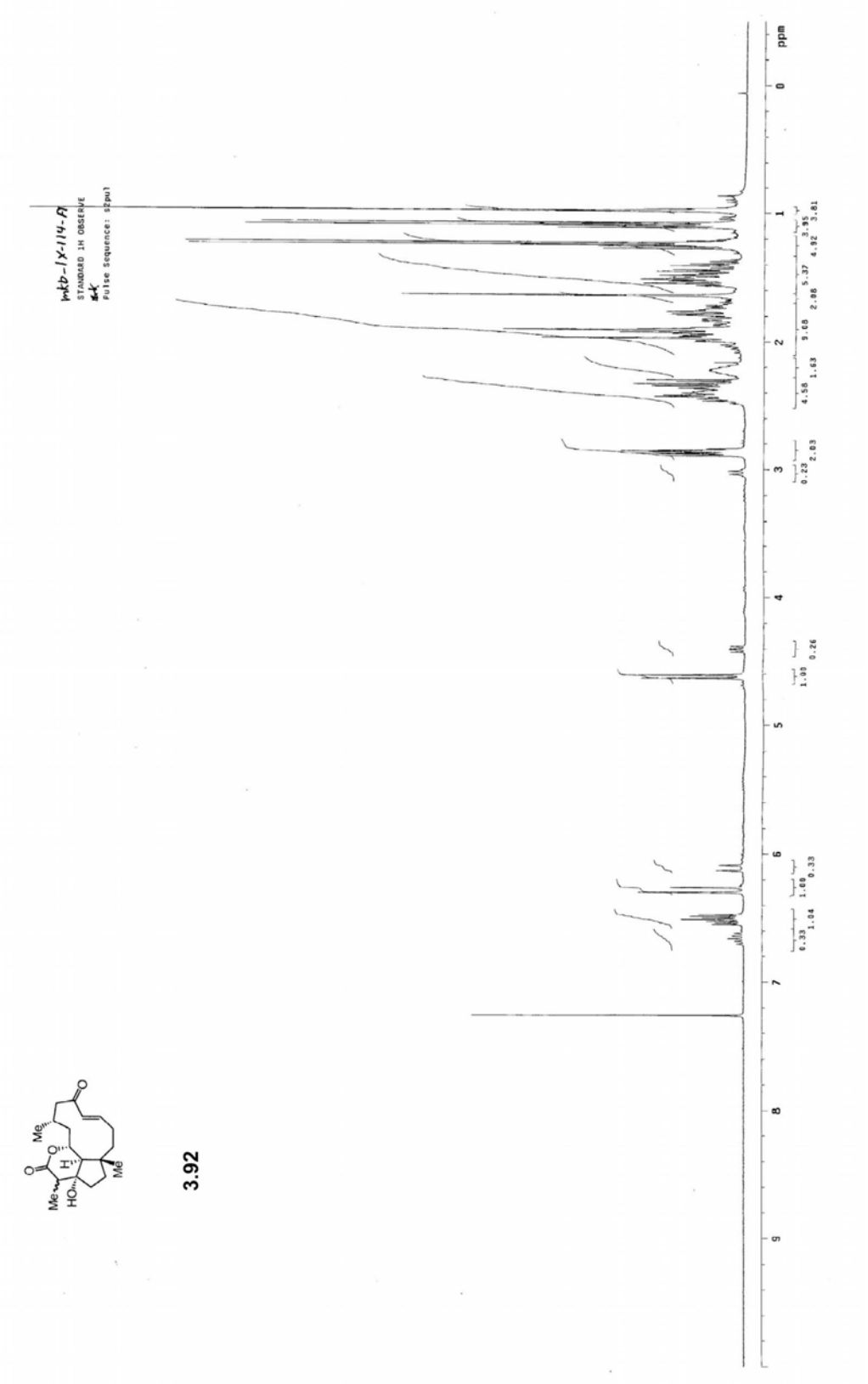
2.52
1.54
2.69
6.84
2.44
3.76
2.44
1.08
13.53


Me
HO
H
O
OSiEt3
Me
3.87
mkb-IX-RCMproduct
Pulse Sequence: s2pul
9
8
7
6
5
4
3
2
1
0
ppm
2.87
1.49
0.65
1.00
0.94
9.00
2.52
6.79
4.90
1.42
1.17
4.15
5.65
14.54
9.54


O
Me
Me
O
H
HO
OTES
Me

3.90

mkb-IX-88-F1
Pulse Sequence: s2pul
9
8
7
6
5
4
3
2
1
0
ppm
0.31
2.92
0.70
1.06
0.49
1.00
0.91
1.44
0.65
6.09
1.78
25.29
8.10
4.03
2.55
21.91
11.12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STANDARD 1H OBSERVE
Pulse Sequence: s2pul
ppm
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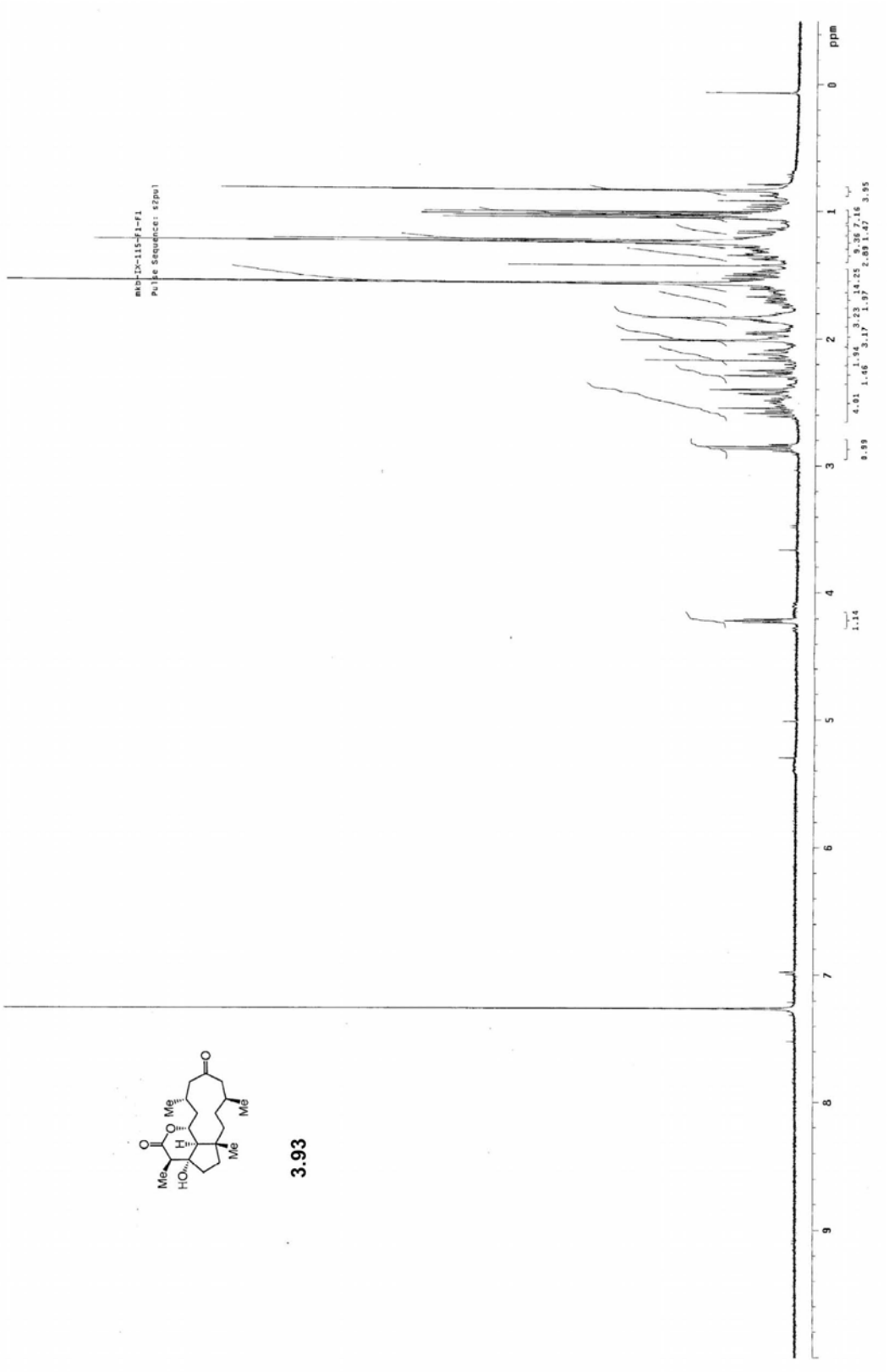
H
HO
Me
Me

3.92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Pulse Sequence: s2pul
ppm
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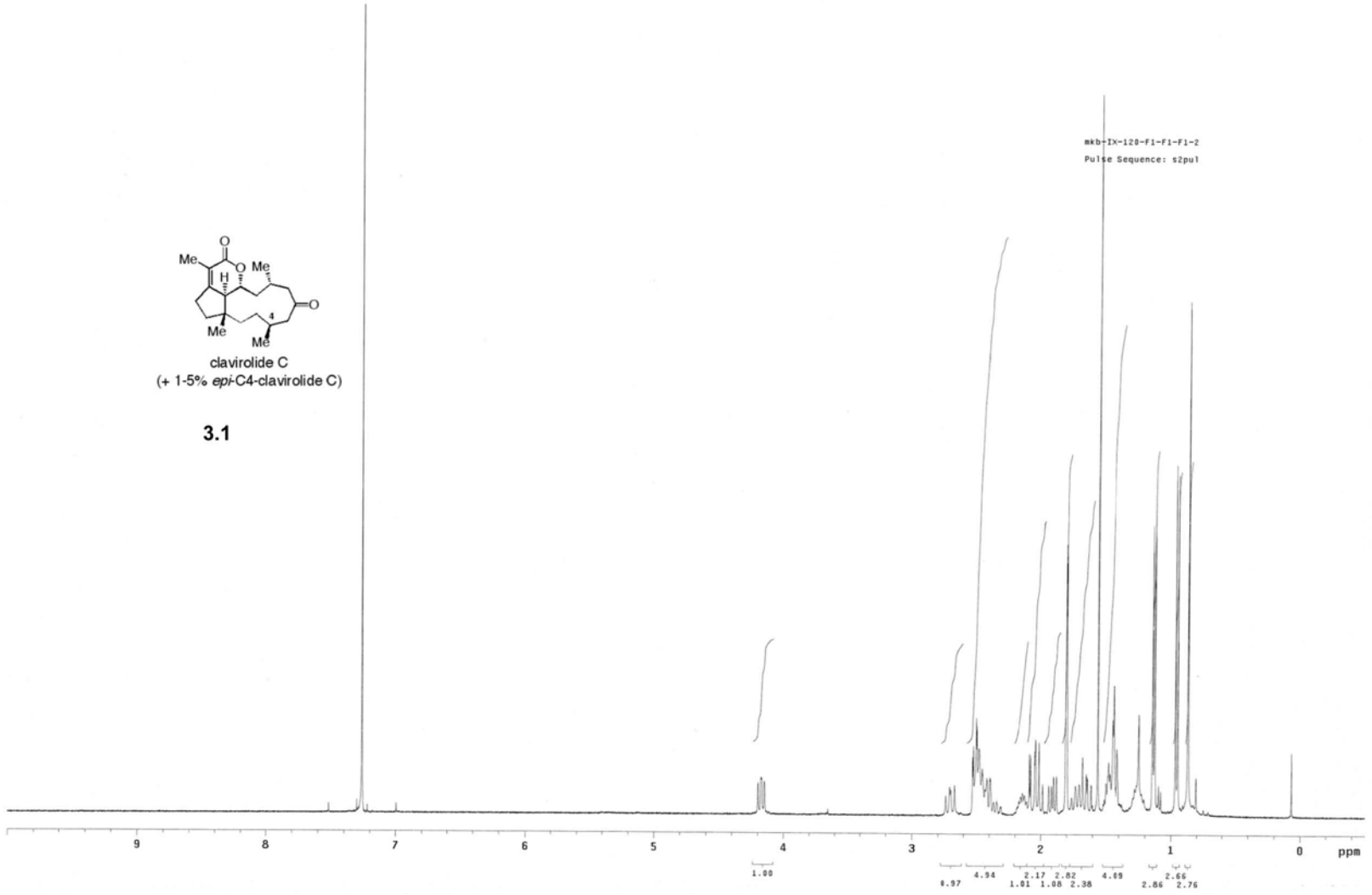
1
2
3
4
5
6
7
8
9
1.14
4.01
1.46
1.94
3.17
3.23
1.97
14.25
2.89
9.36
1.47
7.16
3.95
8.99
Me
Me
Me
Me
H
HO
O
O

3.93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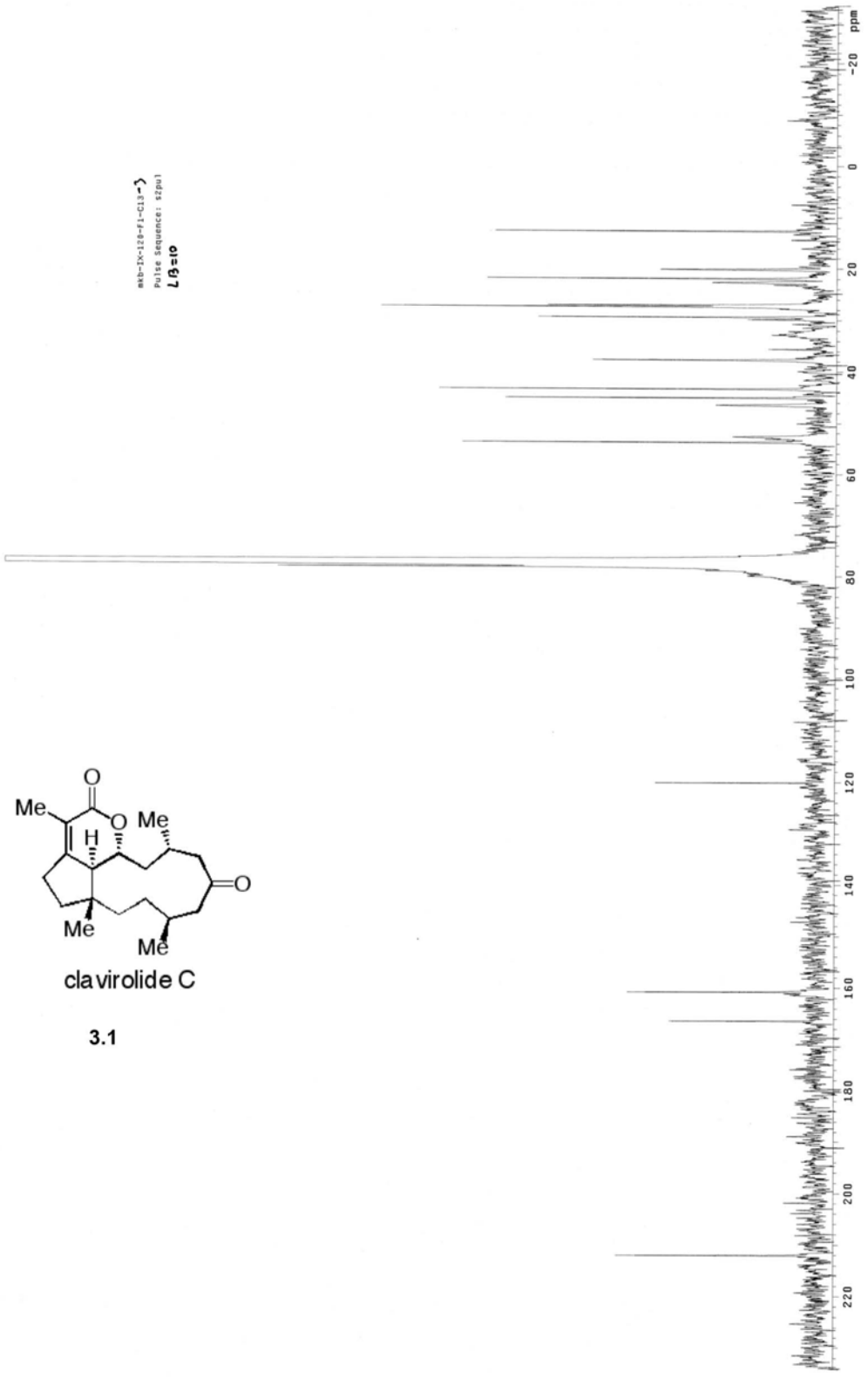
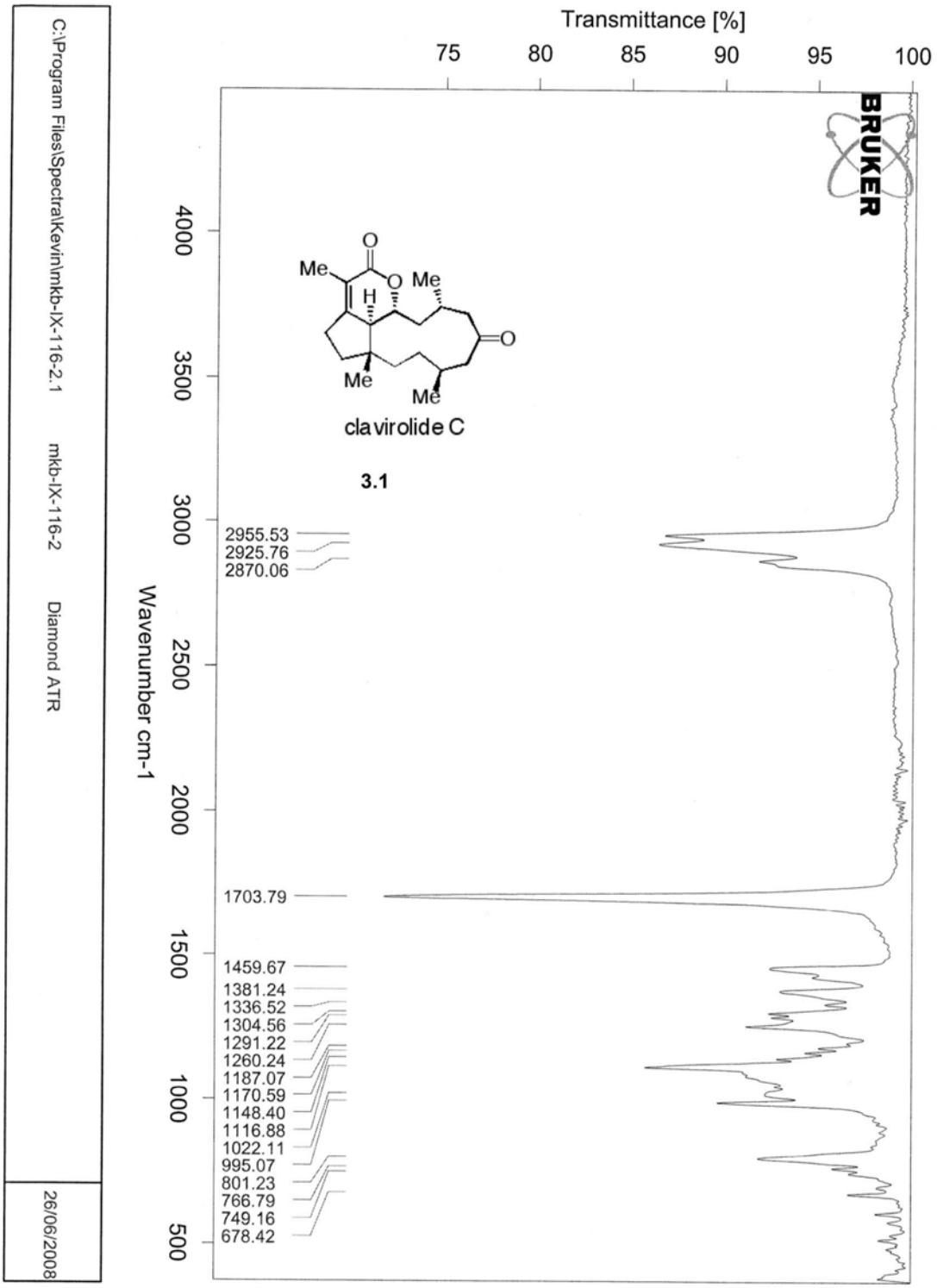
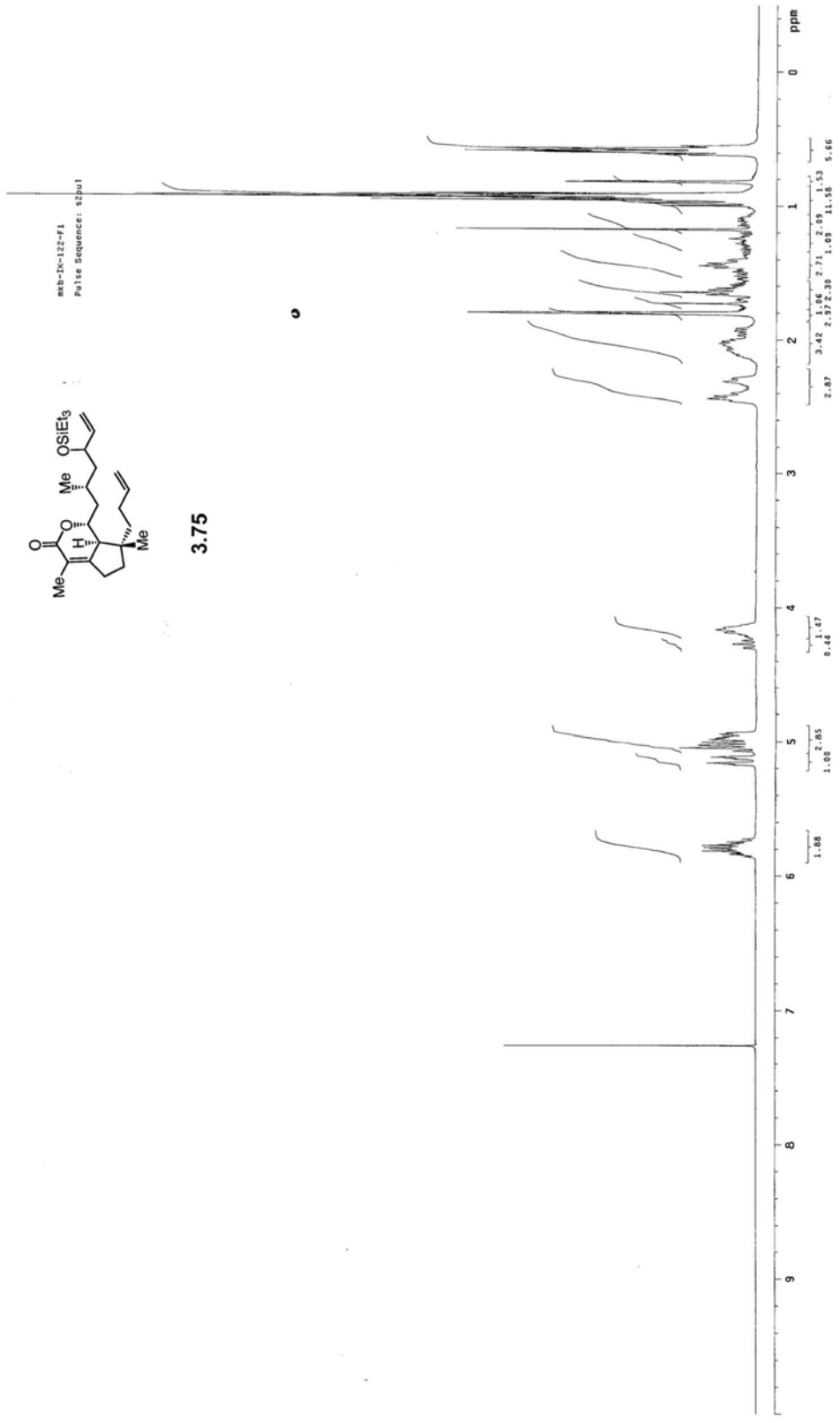
clavirolide C
(+ 1-5% epi-C4-clavirolide C)
3.1
ppm



clavirolide C

3.1


Transmittance [%]
75
80
85
90
95
100
BRUKER
4000
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
O
Me
O
Me
H
O
Me
Me
clavirolide C
3.1
2955.53
2925.76
2870.06
1703.79
1459.67
1381.24
1336.52
1304.56
1291.22
1260.24
1187.07
1170.59
1148.40
1116.88
1022.11
995.07
801.23
766.79
749.16
678.42
C:\Program Files\Spectral\Kevin\mkb-IX-116-2.1
mkb-IX-116-2
Diamond ATR
26/06/2008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Pulse Sequence: s2pul
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Me
O
O
H
Me
Me
3.75
ppm
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1
2
3
4
5
6
7
8
9
1.68
2.85
1.00
1.47
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3.42
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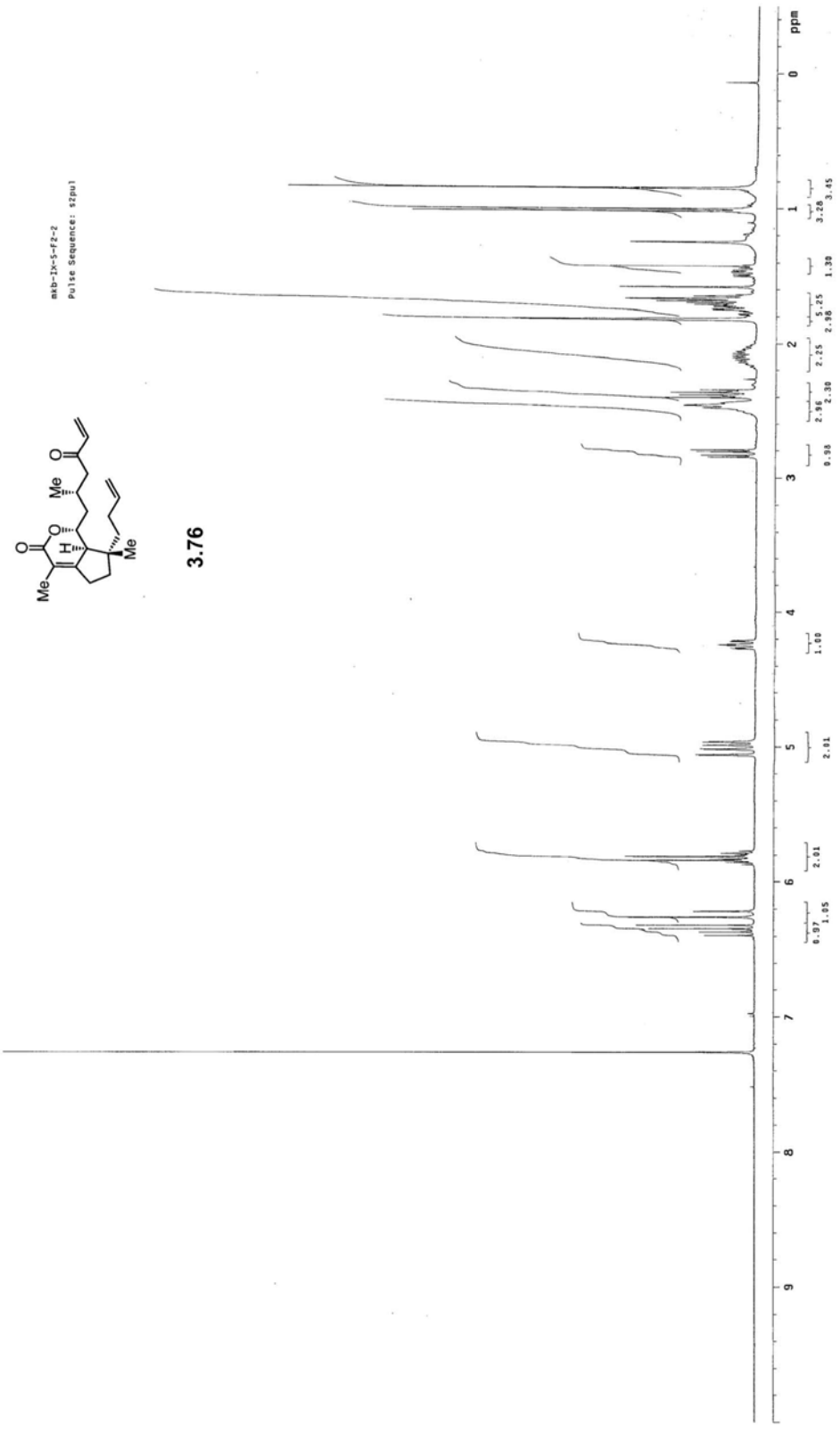
1.66
2.30
2.71
1.69
2.09
11.58
1.53
5.66
2.87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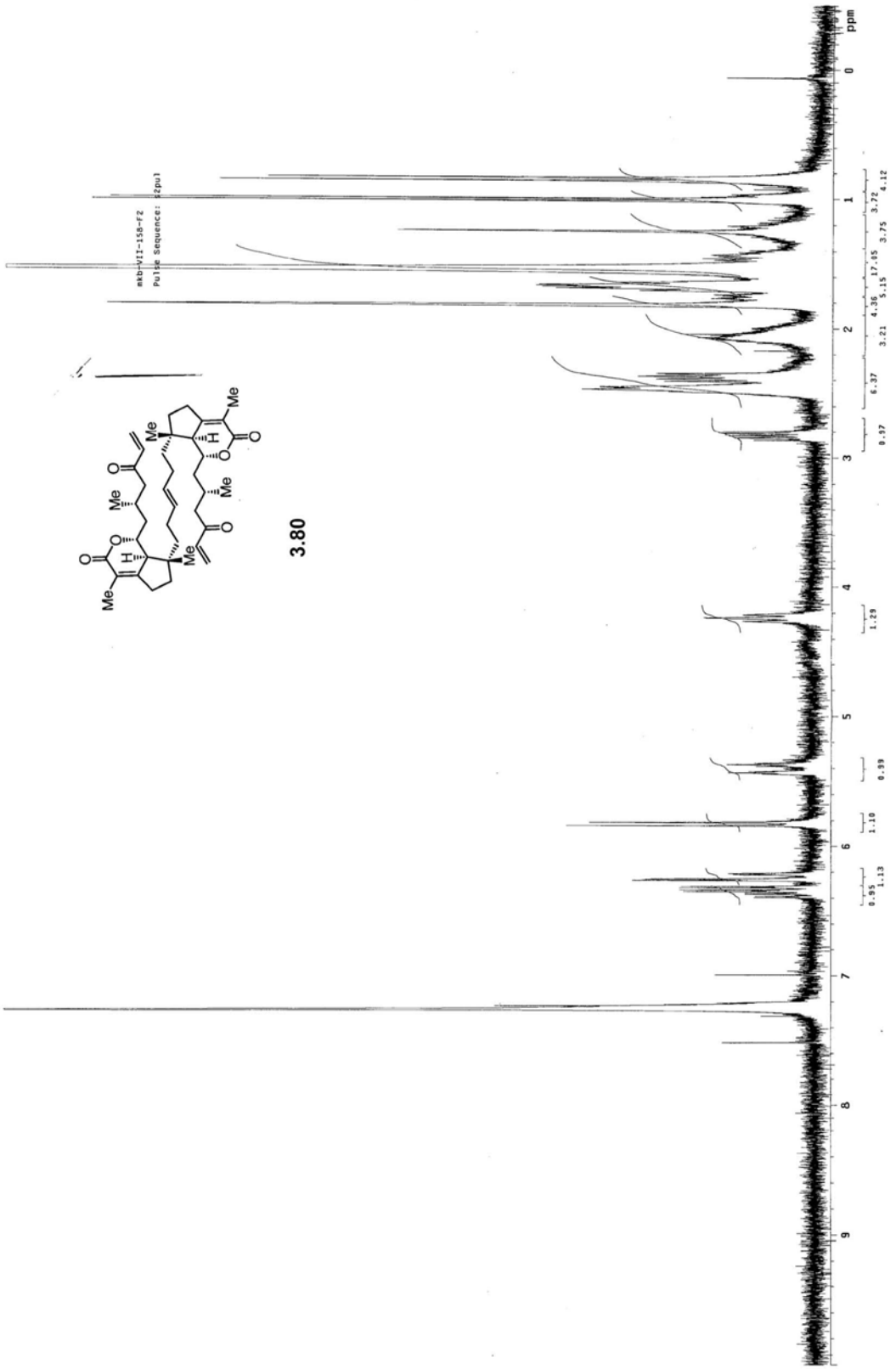
Me
O
O
H
Me
Me
Me
3.76
ppm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ppm
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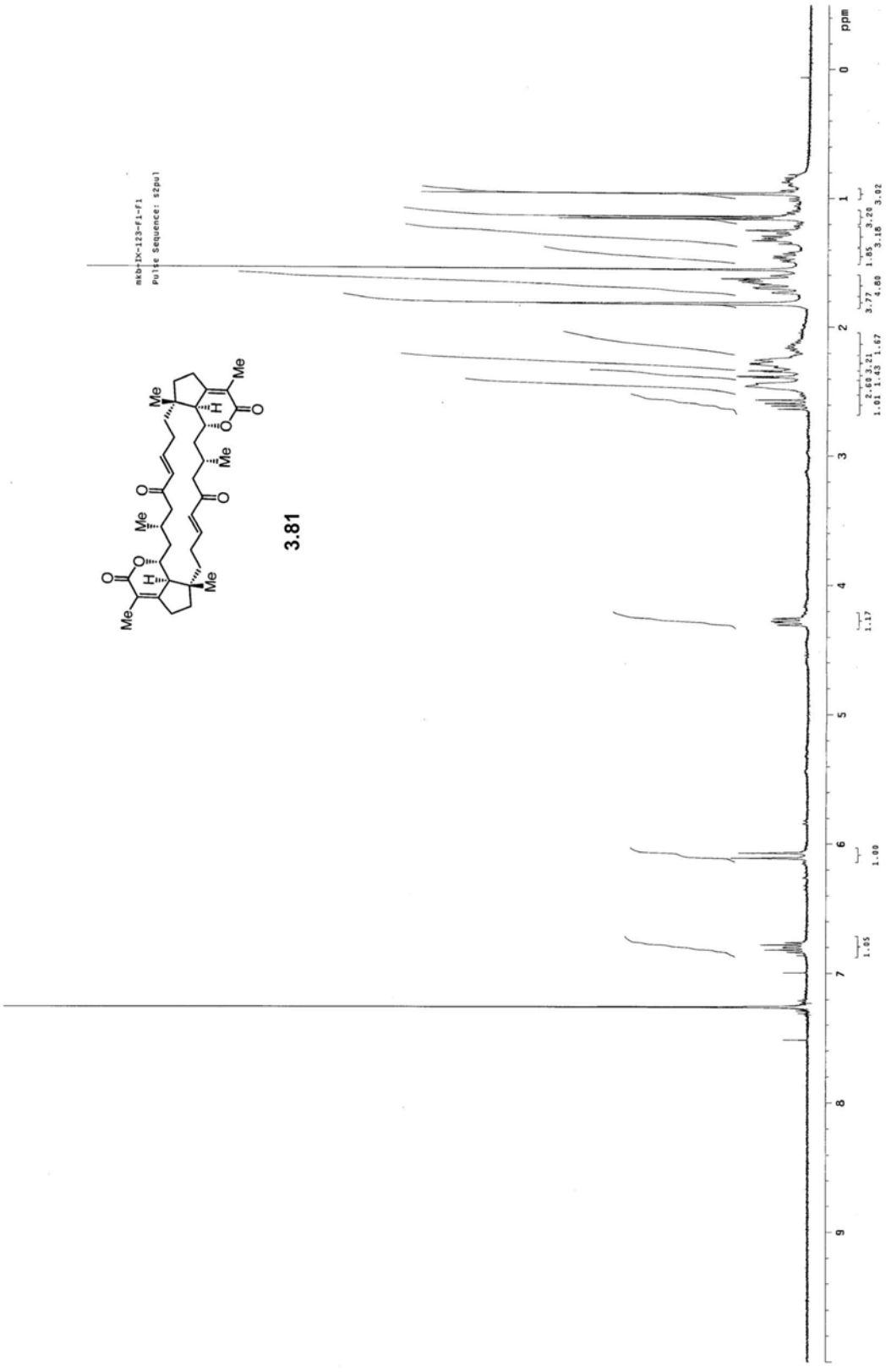
1.13
1.10
0.99
1.29
0.97
6.37
3.21
4.36
5.15
17.85
3.75
3.72
4.12
Me
Me
Me
Me
Me
H
H
O
O
O
O
O
O

3.80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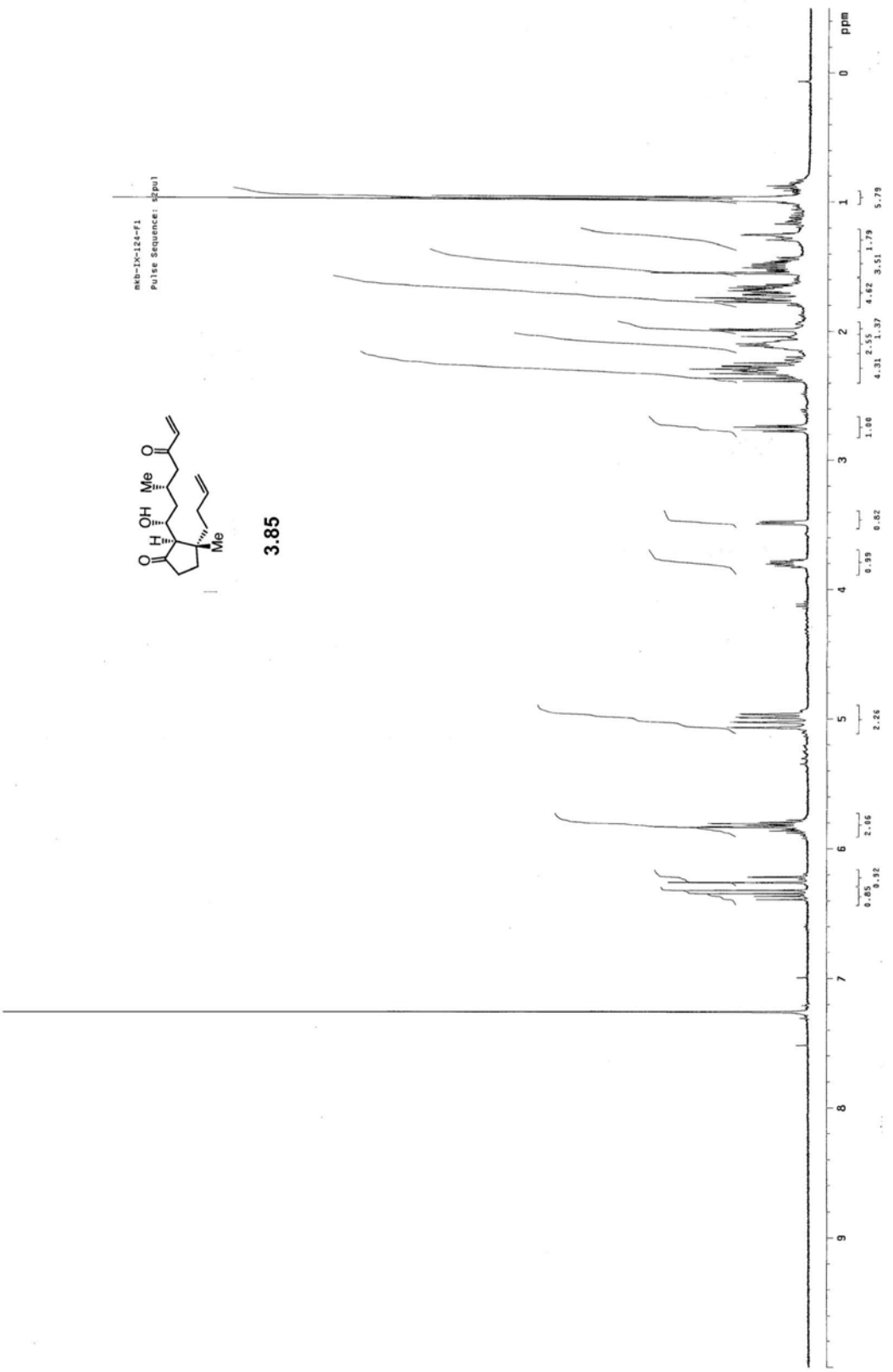
Pulse Sequence: s2pul
Me
Me
Me
Me
Me
Me
O
O
O
O
O
H
H
3.81
ppm
0
1
2
3
4
5
6
7
8
9
1.65
1.00
1.17
2.69
3.21
1.01
1.43
1.67
3.77
4.80
1.85
3.20
3.18
3.02


mxb-1X-124-f1
Pulse Sequence: s2pul
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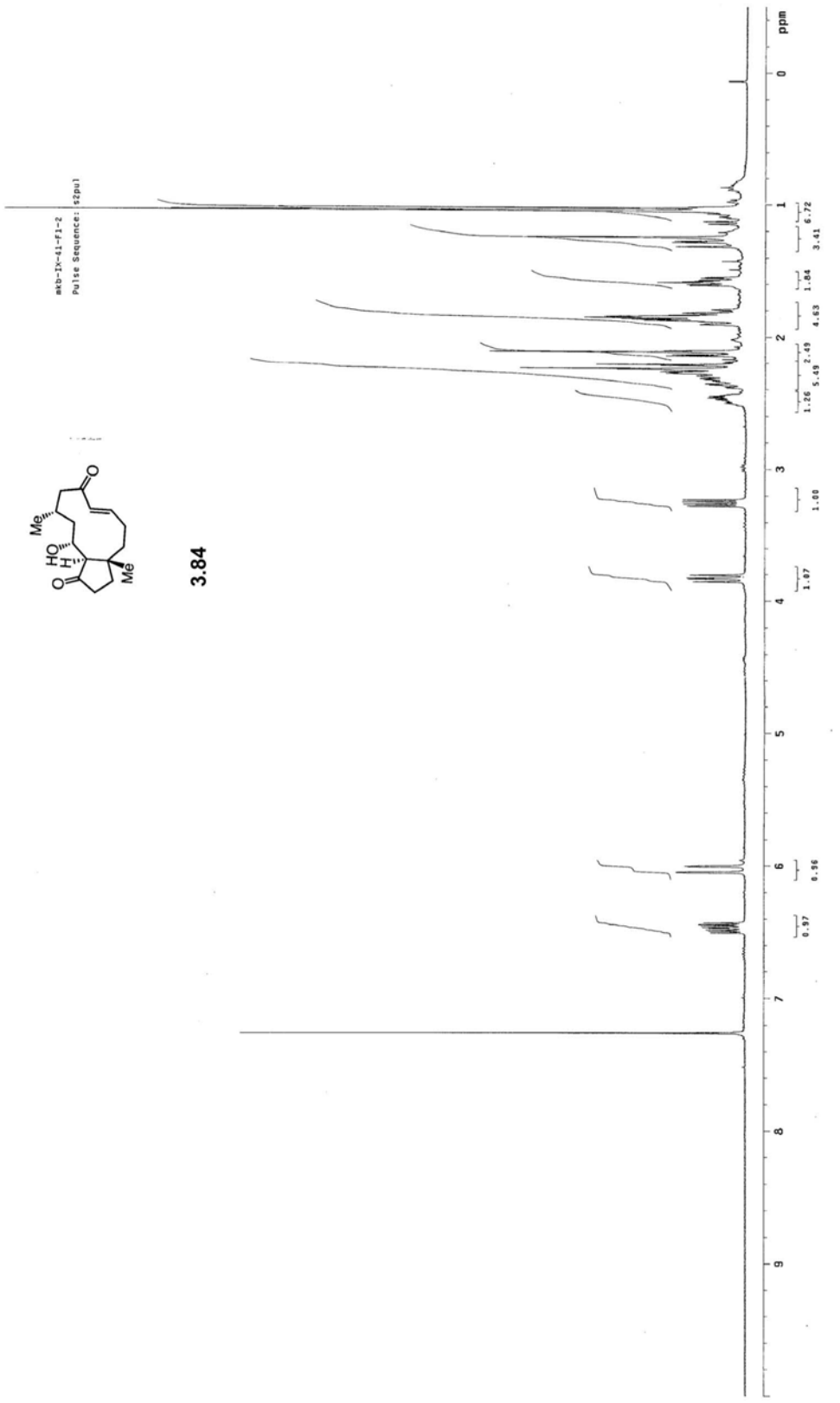
ppm


mkb-IX-41-f1-2
Pulse Sequence: s2pul
Me
HO
H
O
Me
O
3.84
ppm
0
1
2
3
4
5
6
7
8
9
0.97
0.96
1.97
1.00
1.26
5.48
2.49
4.63
1.84
3.41
6.72

mkb-VIII-200-F3
Pulse Sequence: s2pul
3.86
ppm

Chapter 4. Synthesis and Characteristics of Chiral Sulfonate-Based *N*-Heterocyclic Carbene (NHC) Complexes

4.1 *Introduction*

Discovery and development of new chiral catalysts stands as one of the most important objectives in catalytic enantioselective methods development. Loss of the initiative to develop new chiral catalysts often limits the development of methods and frequently denies access to important enantiomerically enriched molecules.

Research in our laboratories has led to the discovery and development of chiral bidentate NHC based ligands **Ag-I**,[194] **Ag-II**[195] and most recently **Ag-III**[196] for use in

(194) (a) "A Recyclable Chiral Ru Catalyst for Enantioselective Olefin Metathesis. Efficient Catalytic Asymmetric Ring-Opening/Cross Metathesis in Air," Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954-4955. (b) "Bidentate NHC-Based Chiral Ligands for Efficient Cu-Catalyzed Enantioselective Allylic Alkylations: Structure and Activity of an Air-Stable Chiral Cu Complex," Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130-11131.

(195) "A Readily Available Chiral Ag-Based N-Heterocyclic Carbene Complex for Use in Efficient and Highly Enantioselective Ru-Catalyzed Olefin Metathesis and Cu-Catalyzed Allylic Alkylation Reactions," Van Veldhuizen, J. J.; Campbell, J. E.; Guidici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877-6882.

(196) (a) "All-Carbon Quaternary Stereogenic Centers by Enantioselective Cu-Catalyzed Conjugate Additions Promoted by a Chiral N-Heterocyclic Carbene," Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097-1100. (b) "Chiral N-Heterocyclic Carbenes in Natural Product Synthesis: Application of Ru-Catalyzed Asymmetric Ring-Opening/Cross-Metathesis and Cu-Catalyzed Allylic Alkylation to Total Synthesis of Baconipyrone C," Gillingham, D. G,; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3860-3864. (c) "Enantioselective Synthesis of Allylsilanes Bearing Tertiary and Quaternary Si-Substituted Carbons through Cu-Catalyzed Allylic Alkylations with Alkylzinc and Arylzinc Reagents," Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554-4558. (d) Highly Site- and Enantioselective Cu-Catalyzed Allylic Alkylation Reactions with Easily Accessible Vinylaluminum Reagents," Lee, Y.: Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H.; *J. Am. Chem. Soc.* **2008**, *130*, 446-447. (e) "Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers by Catalytic Asymmetric Conjugate Additions of Alkyl and Aryl Aluminum Reagents to Five-, Six- and Seven-Membered Ring β-Substituted Cyclic Enones," May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358-7362.

enantioselective Cu-catalyzed alkylation processes (Figure 4.1).[194b,195,196] Recently, a number of methods either reported or currently under development have consistently found **Ag-III**, or related derivatives, to be optimal. This chapter will detail methods to prepare **Ag-III** (as well as analogs) in addition to a discussion regarding structural characteristics of this unique chiral NHC complex.

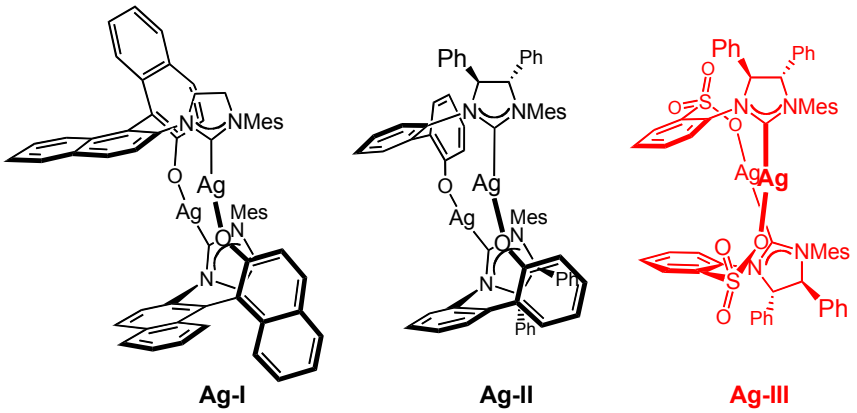


Figure 4.1: Chiral Bidentate NHC Complexes

4.2 *Background*

To extend the scope of Ru-catalyzed enantioselective olefin metathesis processes, we set out to prepare a sulfonate containing *N*-heterocyclic carbene (NHC) Ru complex (i.e., M = Ru, Figure 4.2).[197,198] It was our hope that a less electron donating sulfonate

(197) For review regarding methods for olefin metathesis developed in out laboratory, see: "Ru Complexes Bearing Bidentate Carbenes: From Innocent Curiosity to Uniquely Effective Catalysts for Olefin Metathesis," Hoveyda, A. H.; Gillingham, D. G; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8-23.
(198) For a review regarding synthesis, catalytic activity, and structural characteristics of Ag-NHC complexes, see: (a) "Ag(I) N-Heterocyclic Carbene Complexes: Synthesis, Structure, and Application," Garrison, J. C.; Youngs, W. J. *Chem. Rev.* **2005**, *105*, 3978-4008. For a review regarding general characteristics of carbenes, see: (b) "Stable Carbenes," Bourissou, D.; Guerret, O.; Gabbai, F. P; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39-92. For reviews regarding use of chiral NHC metal complexes for enantioselective catalysis, see: (c) "Chiral *N*-Heterocyclic Carbene-Transition Metal Complexes in Asymmetric Catalysis," Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry,* **2003**, *14*, 951-961. (d) "Chiral

moiety (relative to phenoxy linkages, as in Ru olefin metathesis catalysts derived from **Ag-I** or **Ag-II**, Figure 4.1) would increase the activity of the propagating carbene. While all attempts to prepare the corresponding Ru olefin metathesis catalyst of **Ag-III** failed, these studies led us to uncover a new procedure for the formation of imidazolinium salts as well as a new chiral ligand for highly enantioselective and efficient Cu-catalyzed alkylation reactions.[199]

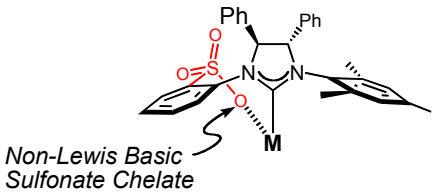


Figure 4.2: Proposed chiral NHC complex

4.3 *Synthesis of Sulfonate Based NHC Complexes*

4.3.a Preparation of Ag-III

We envisioned that imidazolinium salt **III** (precursor to complex **Ag-III**, Figure 4.1) might be prepared in an analogous manner to previously reported methods[195] from commercially available, enantiomerically pure diamine **4.1 (**Scheme 4.1**)**. Palladium-catalyzed coupling of diamine **4.1** with bromide **4.2** (prepared in one step from

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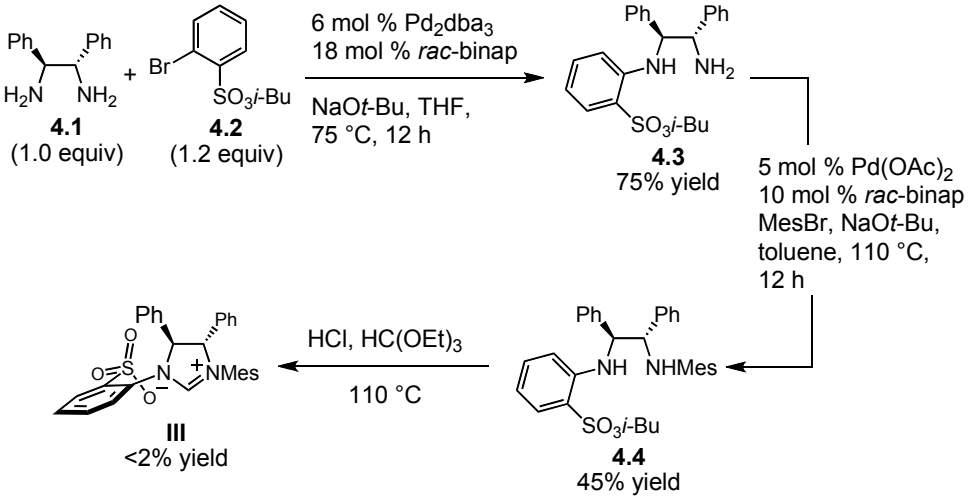
N-Heterocyclic Carbenes as Stereodirecting Ligands in Asymmetric Catalysis," César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619-636. (e) Metal-mediated Asymmetric Alkylation using Chiral *N*-Heterocyclic Carbenes Derived from Chiral Amines," Douthwaite, R. E. *Coord. Chem. Rev.* **2007**, *251*, 702-717.

(199) (a) "Recent Advances in Catalytic Enantioselective Michael Additions," Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171-196. (b) "Enantioselective Copper-Catalysed Conjugate Addition," Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221-3236. (c) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. in *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, pp. 224-258. (d) "Recent Advances in Metal-Catalyzed Asymmetric Conjugate Additions," Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279-1300.

commercially available materials), mediated by $Pd_2(dba)_3$ and *rac*-binap in THF at 75 °C, afforded **4.3** in good yield (75%).[200b] A second C-N bond formation in the presence of $Pd(OAc)_2$ and *rac*-binap in toluene at 110 °C furnished dissymmetrical diamine **4.4** in 45% yield.[200a] This sequence readily provided gram quantities of **4.4** in a time efficient manner.

Scheme 4.1: Preparation of Diamine **4.4**

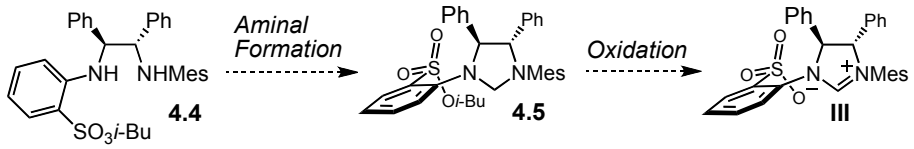


Under standard imidazolinium salt formation conditions (HCl, $HC(OEt)_3$, 110 °C)[201] only decomposition of the substrate was observed (>98% consumption of starting material, Scheme 4.1). We therefore decided to pursue an alternative two-step strategy,

(200) (a) "Scope and Limitations of the Pd/BINAP-Catalyzed Amination of Aryl Bromides," Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144-1157. (b) "Palladium Catalysed Mono-*N*-Arylation of Enantiopure Diamines," Frost, C. G.; Mendonça, P. *Tetrahedron: Asymmetry* **1999**, 10, 1831-1834.
(201) "Imidazolylidenes, Imidazolinylidenes and Imidazolidines," Arduengo, A. J.; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. *Tetrahedron*, **1999**, *55*, 14523-14534.

outlined in Scheme 4.2, whereby the imidazolinium salt **III** may be obtained through oxidation of aminal **4.5**.[202]

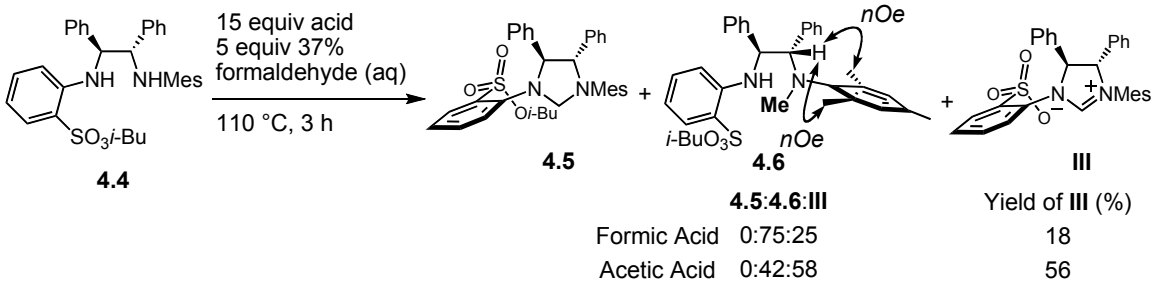
Scheme 4.2: Revised Route for the Preparation of Imidazolinium Salt **III** through Oxidation of Aminal **4.5**



As illustrated in Scheme 4.3, under conditions outlined by Roland and coworkers for synthesis of aminals from 1,2 diamines bearing *only N-alkyl substitutents* (formic acid, formaldehyde (aq), 110 °C, 3 h),[203] diamine **4.4** was converted not to the expected aminal **4.5** (<2% observed) but rather to imidazolinium salt **III**, albeit in low isolated yield (18%). The majority of the unpurified reaction mixture (75%) contained *N*-Me diamine **4.6** (<2% of the regioisomeric *N*-Me product was observed). We reasoned that thermal decomposition of formic acid might generate hydride necessary for the formation of **4.6**. Thus, replacement of formic acid with acetic acid led to a substantial improvement in yield of isolated **III** (56%); however, **4.6** was still generated in significant quantities (42% of the crude reaction mixture).

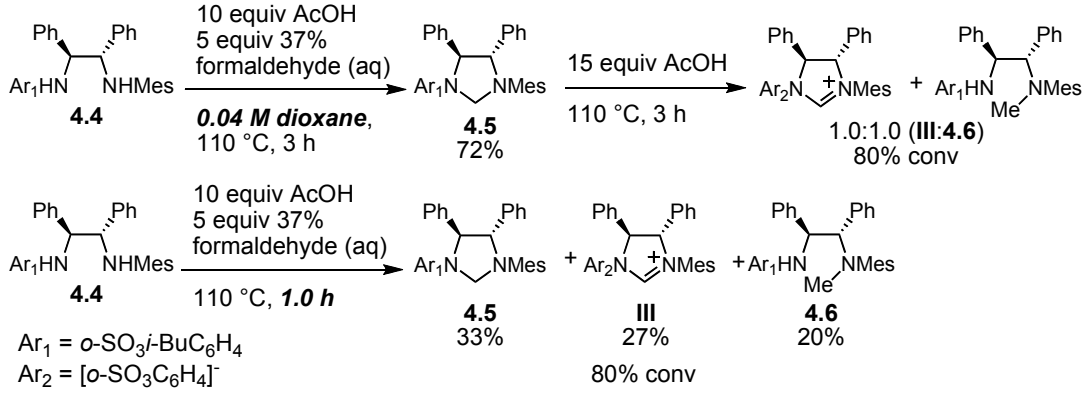
(202) (a) "Unusually Facile Palladium Catalysed Oxidation of Imidazolidines and Oxazolidines," Alexakis, A.; Aujard. I.; Pytkowicz, J.; Roland, S.; Mangeney, P. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 949-951. (b) "Synthesis of Chiral Silver(I) Diamino Carbene Complexes from (*R*,*R*)-4,5-Di-*tert*-Butylimidazoline," Pytkowicz, J.; Roland, S.; Mangeney, P. *J. Organomet. Chem.* **2001**, *631*, 157-163.
(203) "A Practical and Efficient Synthesis of Enantiomerically Pure Di-*tert*-butyl-ethanediamine," Roland, S.; Mangeney, P.; Alexakis, A. *Synthesis*, **1999**, *2*, 228-230.

Scheme 4.3: Unexpected Synthesis of Imidazolinium Salt **III**



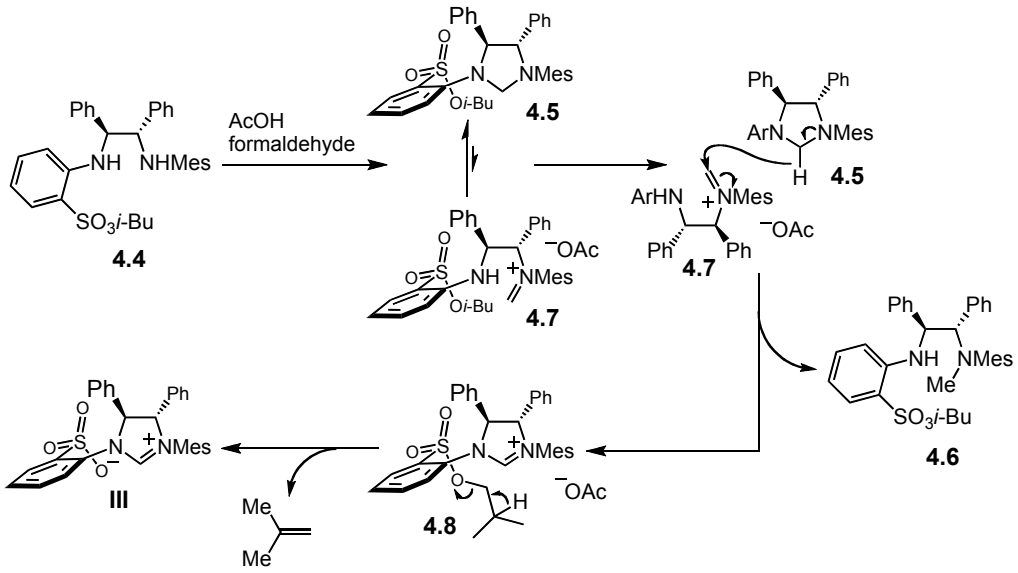
During these studies we observed, as illustrated in Scheme 4.4, that cyclization of **4.4** performed in dioxane (0.04 M), under otherwise identical conditions to those shown in Scheme 4.3, led to the formation of aminal **4.5** as the sole product (<2% imidazolinium salt **III** detected). Furthermore, simply heating a solution of aminal **4.5** in AcOH (15 equiv) furnished a 1.0:1.0 mixture of imidazolinium salt **III** and *N*-Me product **4.6** (80% conv), suggesting aminal **4.5** is an intermediate during the synthesis of **III**. It may be possible, therefore, to observe **4.5** if the reaction, when performed in the absence of solvent, is quenched early. Indeed, if the reaction was stopped after only 1 h (vs. 3 h to obtain >98% conv), 33% of the unpurified reaction mixture contained aminal **4.5** along with **III** and **4.6** in 27% and 20%, respectively (80% conv, Scheme 4.4).

Scheme 4.4: Evidence for the Intermediacy of Aminal **4.5**



Based on the studies illustrated in Scheme 4.4, we propose a mechanism for this process, involving a hydride transfer (Scheme 4.5).[204] Formation of aminal **4.5** occurs readily upon exposure to AcOH and formaldehyde, which is likely in equilibrium with iminium ion **4.7** at 110 °C. Extrusion of a hydride from aminal **4.5**, assisted by the neighboring nitrogen lone pairs, followed by reduction of the iminium ion **4.7** leads to **4.8** and **4.6**, respectively. Elimination of 2-methylpropene from **4.8** furnishes the desired imidazolinium salt **III**.

Scheme 4.5: Plausible Mechanism for the Formation of **III** and **4.6** Involving Hydride Transfer



This mechanism accounts for all of the above observations: (1) When the reaction is performed in dioxane the occurrence of hydride transfer was reduced due to dilution. (2) Based on the proposed mechanism in Scheme 4.5, a 1.0:1.0 ratio of **III** and **4.6** should

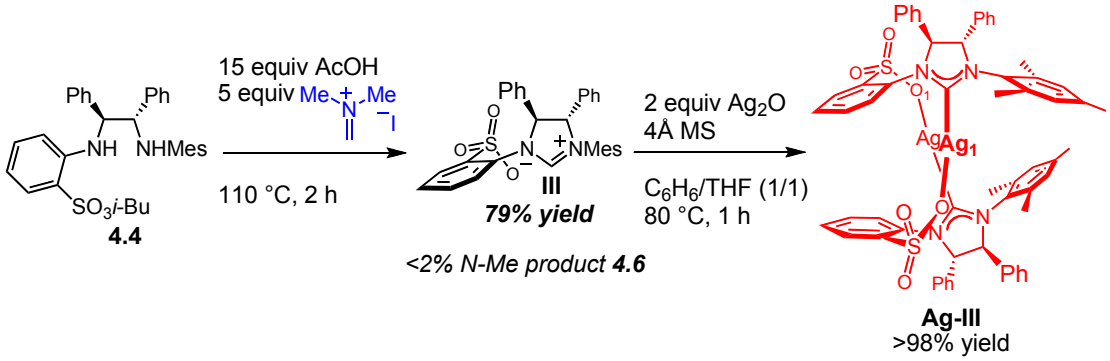
(204) For a related mechanism, see: "Chemical Transformations of 7,9-Disubstituted Purines and Related Heterocycles. Selective Reductions of Imines and Immonium Salts," Hecht, S. H.; Adams, B. L.; Kozarich, J. W. *J. Org. Chem.* **1976**, *41*, 2303-2311.

be expected. However, imidazolinium salt formation in the presence of formaldehyde and AcOH (vs. direct formation of **III** from isolated **4.5** in the presence of *only* AcOH) resulted in a mixture of **III** and **4.6** *always* favoring imidazolinium salt **III** (1.4:1.0). To account for this discrepancy we propose that formaldehyde likely competes with **4.7** as the hydride acceptor, thus giving rise to a product mixture enriched in desired product **III**. As expected, cyclization in the absence of formaldehyde (**4.5**→**III**) afforded a 1.0:1.0 mixture of **III** and **4.6 (**Scheme 4.4).

Armed with a better understanding of the reaction mechanism, we reasoned that cyclization carried out in the presence of a preformed iminium-based hydride acceptor in excess would compete with **4.7** and thus lead to higher yield of **III**. Eschenmoser's salt[205] seemed perfectly suited for this task. Replacement of formaldehyde with Eschenmoser's salt led to clean conversion to **III** in 79% isolated yield (Scheme 4.6). It is noteworthy that <2% of *N*-Me product **4.6** is detected in the unpurified reaction mixture reinforcing the proposed mechanism. Imidazolinium salt **III** could be cleanly converted to **Ag-III** in >98% yield.

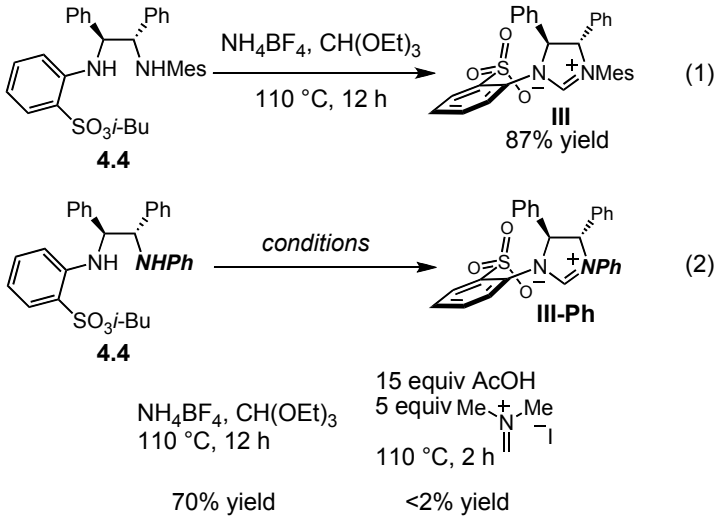
(205) "Dimethyl(methylene)ammonium Iodide," Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330-331.

Scheme 4.6: Improved Synthesis of Imidazolinium Salt **III** and Conversion to Ag(I)-NHC complex **Ag-III**



Subsequent to the above studies, it was discovered that cyclization of diamine **4.4** could be effected by $CH(OEt)_3$ and NH_4BF_4 to provide imidazolinium salt **III** in 87% yield. Extended reaction times were necessary (12 h) to effectively cleave the *i*-Bu unit. Neither the method illustrated in Scheme 4.6 (Eschenmoser salt, AcOH) nor the reaction shown in Scheme 4.7, eq (1) ($CH(OEt)_3$, NH_4BF_4) are significantly superior to the other for preparation of **III**. In one particular example, however, cyclization to provide **III-Ph**, must be carried out with $CH(OEt)_3$ and NH_4BF_4, as the analogous reaction with Eschenmoser's salt and AcOH failed to deliver the desired product (>98% consumption of substrate, <2% yield, Scheme 4.7, eq (2)).

Scheme 4.7: Cyclization of Diamines with NH_4BF_4 and $CH(OEt)_3$



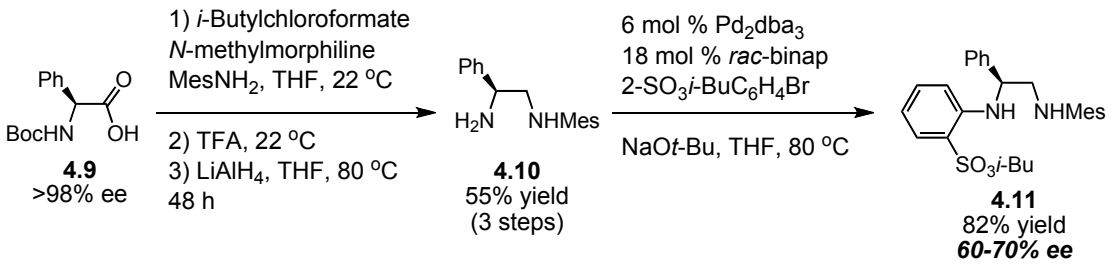
4.3.b Preparation of Ag-IV (Des-Ph Ag-III)

During our studies directed towards Cu-catalyzed ACA of trialkylaluminum reagents to β-substituted cyclopentenones, **Ag-IV** (see, Scheme 4.9), a chiral sulfonate-based ligand in which a phenyl group on the chiral NHC is omitted, was discovered to provide the ACA products in higher selectivity than additions promoted by **Ag-III**. Therefore, an efficient and scaleable synthesis of **Ag-IV** (and its derivatives) was deemed necessary.

Synthesis of new chiral NHC **Ag-IV** commenced with coupling of mesityl aniline and Boc-Phg (**4.9**) followed by Boc deprotection and $LiAlH_4$ reduction to afford diamine **4.10** in 55% yield over 3 steps (Scheme 4.8). Pd-catalyzed C-N bond coupling proceeded smoothly to furnish **4.11** in good yield (82%). The enantiomeric purity of diamine (**4.11**),

however, was found to be 60-70% ee.[206] Epimerization was thought to occur primarily during the $LiAlH_4$ reduction in refluxing THF. All attempts to perform the reduction at lower temperature (22 °C) or to use alternative reducing agents (BH_3•SMe_2, dibal-H), delivered **4.10** in varying degrees of enantiopurity (~70% ee) or with low efficiency (<40% conv).[207] Based on these studies, we decided to pursue a route that does not involve phenylglycine.[208]

Scheme 4.8: Attempted Synthesis of **Ag-IV**

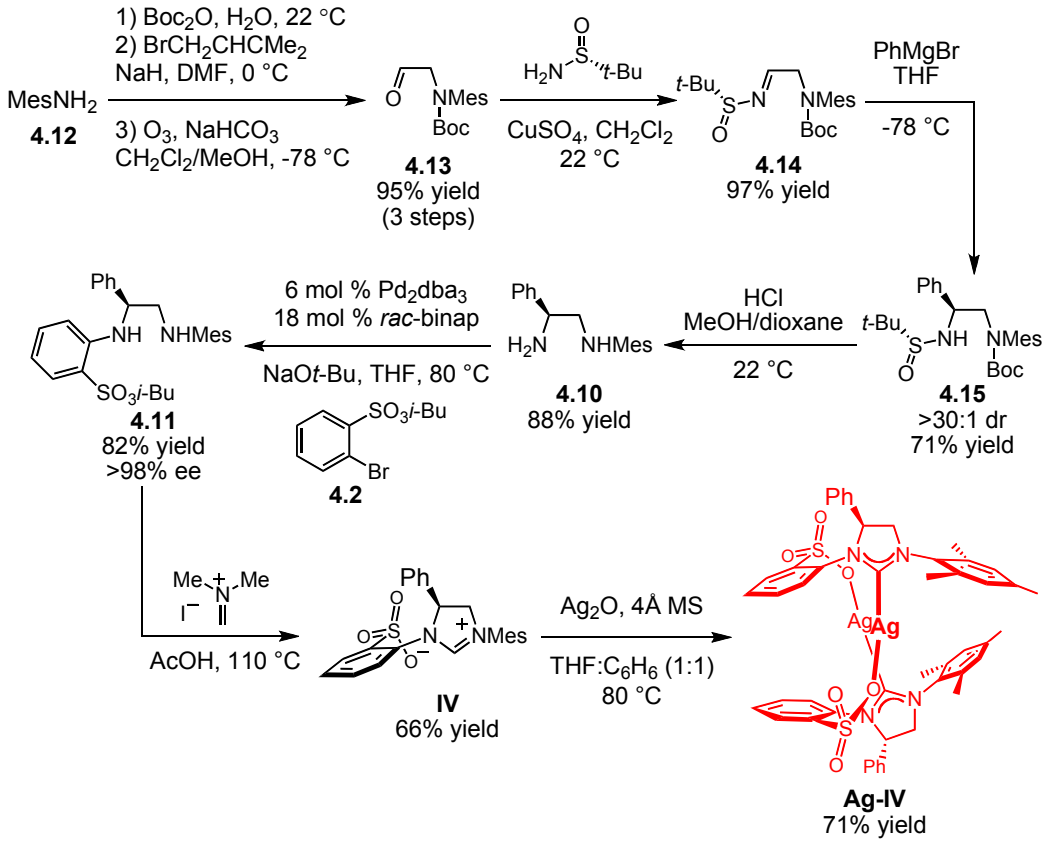


Based on the shortcomings of the route depicted in Scheme 4.8, we decided to pursue a new strategy utilizing a diastereoselective imine arylation developed by Ellman and coworkers (Scheme 4.9).[209] Condensation of aldehyde **4.13** (prepared in three steps from mesityl aniline (**4.12**))[194] with commercially available (*R*)-*tert*-butanesulfinamide afforded imine **4.14** in 97% yield. Addition of PhMgBr to imine **4.14** in THF at –78 °C delivered the sulfinamide **4.15** as a single diastereomer in 71% yield. Deprotection of the Boc and

(206) A similar sequence of reactions has been carried out beginning with Boc-Val; <2% reduction in enantiopurity was observed. "Design and Synthesis of Imidazolinium Salts Derived from (L)-Valine. Investigation of their Potential in Chiral Molecular Recognition," Clavier, H.; Boulanger, L.; Audic, N.; Toupet, L.; Mauduit, M.; Guillemin, J-C. *Chem. Commun.* **2004**, 1224-1225.
(207) Attempted recrystallization of diamine **4.11** or the corresponding imidazolinium salt to enantiomeric purity was unsuccessful.
(208) Another potential route to **Ag-IV** could involve reductive amination of phenylglycinal and mesityl aniline. However, it has been reported the phenylglycinal is unstable and epimerizes upon workup or standing at 22 °C. "Synthesis of Taxol and Taxotere Side Chains by 2-(Trimethlsilyl)thiazole based Homologation of L-Phenylglycine," Dondoni, A.; Perrone, D.; Semola, T. *Synthesis*, **1995**, 181-186.
(209) (a) "*N*-*tert*-Butanesulfinyl Imines: Versatile Intermediates for the Asymmetric Synthesis of Amines," Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984-995. (b) "Highly Diastereoselective and Enantioselective Addition of Organometallic Reagents to a Chiral C_2-Symmetrical Bisimine," Sun, X.; Wang, S.; Sun, S.; Zhu, J.; Deng, J. *Synlett* **2005**, *18*, 2776-2780.

sulfinamide groups with HCl in MeOH delivered diamine **4.10** after basic work-up. Pd-catalyzed C-N bond coupling furnished **4.11** (>98% ee by chiral HPLC analysis) in good yield (82%). Cyclization of diamine **4.11** with Eschenmoser's salt in AcOH delivered imidazolinium salt **IV** in 66% yield. Treatment of **IV** with Ag_2O in refluxing THF/C_6H_6 provided **Ag-IV** in 71% yield. While this route did provide **Ag-IV**, the current synthesis requires nine steps, and thus we continued to search for a more efficient route.

Scheme 4.9: 1st Generation Synthesis of **Ag-IV**



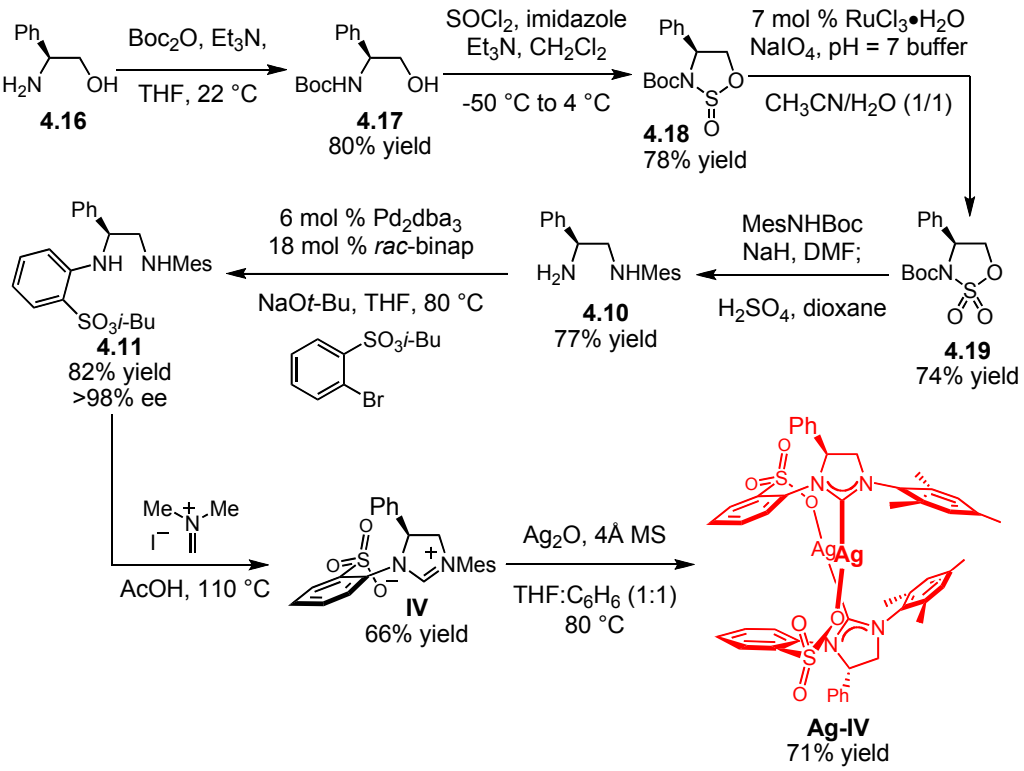
A revised synthesis of **Ag-IV** based on ring opening of sulfamidates is illustrated in Scheme 4.10. [210,211] Cyclization of Boc-phenylglycinol (**4.17**, prepared in one step)

(210) Similar studies for preparing chiral monodentate NHCs were carried out by Adil Zhugralin.

with $SOCl_2$, imidazole and Et_3N provided sulfamidite **4.18** in 78% yield. It is important to note that slow addition of Boc-phenylglycinol (**4.17**) was necessary to achieve high yield as rapid addition delivered significant quantities of a sulfoxide dimer. Catalytic oxidation of sulfamidite promoted by $RuCl_3$ provided sulfamidate (**4.19**) in 74% yield. Subjection of sulfamidate **(4.19**) to a solution of MesNHBoc, pretreated with NaH in DMF, followed by treatment with H_2SO_4 furnished diamine **4.10** in 77% yield. Diamine **4.10** was transformed to **Ag-IV** as previously discussed (see above, Scheme 4.9). This route (Scheme 4.10) is more efficient (7 vs. 9 steps) and amenable to scale (2 g of **Ag-IV** has been prepared) than the route illustrated in Scheme 4.9.

(211) For similar sequences that employ ring opening with sulfamidates with amines, see: (a) "Synthesis of the *Kappa-Agonist* CJ-15,161 via a Palladium-Catalyzed Cross-Coupling Reaction," Ghosh, A.; Sieser, J. E.; Caron, S.; Watson, T. J. N. *Chem. Commun.* **2002**, 1644-1645. (b) "Enantiopure 1,4-Benzoxazines via 1,2-Cyclic Sulfamidates. Synthesis of Levofloxacin," Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Lett.* **2007**, *9*, 3283-3286.

Scheme 4.10: 2nd Generation Synthesis of **Ag-IV**



4.4 *Characteristics of Sulfonate Based NHC Complexes*

The steric and electronic differences between phenoxy based NHC complexes (i.e., **Ag-I** and **Ag-II**) and sulfonate based NHC complexes (i.e., **Ag-III** and **Ag-IV**) are significant. These differences have likely allowed the latter complexes to be uniquely effective in many cases where the former complexes failed.

The benzylic proton proximal to the sulfonate moiety is significantly shifted downfield (δ = 6.55 ppm) as compared to the analogous benzylic proton in phenoxy-based complex **Ag-II** (δ = 5.36 ppm) (Figure 4.3). This suggests the electron withdrawing sulfonate unit significantly affects the electronic nature of the NHC. While

studies to determine how this electronic perturbation influences the nature of the carbene-[M] bond in **Ag-III** have not yet been carried out, a report by Plenio and coworkers might shed light on this situation.[212] As illustrated in Figure 4.4, iridium carbonyl complexes bearing NHCs with different electronic properties were prepared. The ν(CO) stretching frequencies were measured to evaluate the relative donating ability of each NHC. The NHC bearing electron withdrawing *p*-SO_2tol units was found to be the least electron donating ligand analyzed suggesting that the NHC unit of **Ag-II** is a stronger electron donor than that of **Ag-III**.

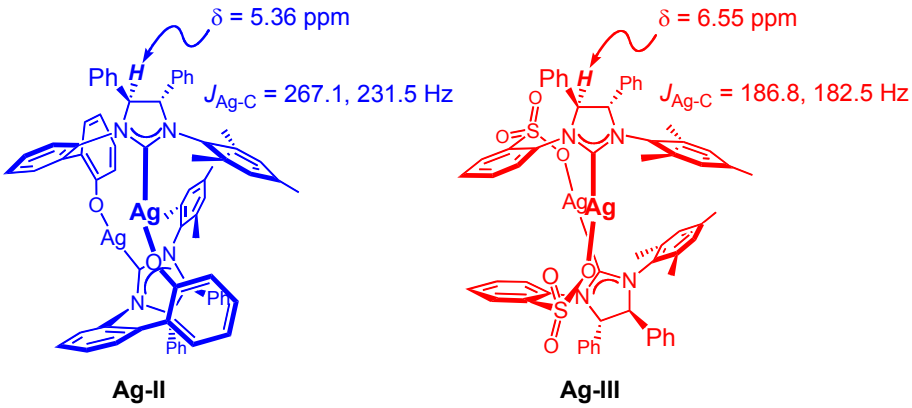
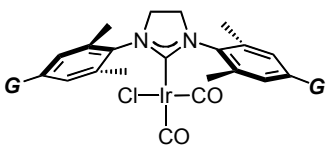


Figure 4.3: Electronic Properties of Ag-II and Ag-III



G	*υ (CO) [cm^{-1}]*
NEt_2	1978, 2064
H	1981, 2067
SO_2tol	1985, 2074

Figure 4.4: Electronic Properties of $NHCIrCl(CO)_2$

(212) "Tuning the Electronic Properties of N-Heterocyclic Carbenes," Leuthäußer, S.; Schwarz, D.; Plenio, H. *Chem. Eur. J.* **2007**, *13*, 7195-7203.

Furthermore, the Ag-carbon coupling constants of **Ag-III** ($J_{Ag\text{-}C}$ = 186.8 and 182.5 Hz) are significantly less than those of **Ag-II** ($J_{Ag\text{-}C}$ = 267.1 and 231.5 Hz, Figure 4.3). Coupling constants between two nuclei can be a measure of internuculear distance, these data suggest that in solution the Ag-$C_{carbene}$ of **Ag-III** is longer than that of **Ag-II**.[213] These data are consistent with the above conclusion that **Ag-III** is a less σ-donating NHC than **Ag-II**.

Unlike Ag-NHC complex **Ag-II**, which contains an eight membered ring chelate, Ag-NHC complex **Ag-III** bears a more geometrically constrained seven membered chelate (for steric considerations, monomeric chiral NHC complexes are likely the active catalysts). Furthermore, in the monomeric state, the sulfonate linkage may not be covalently bound to the metal center (O-Ag 3.83 Å for **Ag-III** vs. 2.70 Å for **Ag-II**, values from the X-ray crystal structure, Figure 4.5).

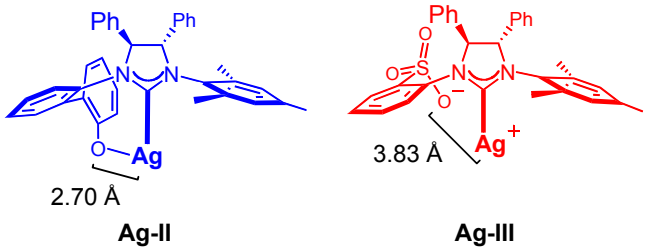


Figure 4.5: Monomeric Ag-NHC Complexes

In order for the sulfonate unit to effectively coordinate (as in **Ag-III Anti**, Figure 4.6**)** with the metal center, the proximal C-N bond must rotate. It is likely that steric interaction between H_a and the neighboring phenyl ring disfavor this mode of coordination. Therefore, since the sulfonate unit is small, relative to a phenoxy group as

(213) In the crystalline state the Ag-$C_{carbene}$ bond lengths of **Ag-III** (2.087 Å) and **Ag-II** (2.068 Å) are similar.

in **Ag-II**, syn-to-phenyl group complexation can occur (i.e., **Ag-III Syn**). Evidence for this mode of coordination has been observed in a related X-ray crystal structure **(Zn-III)**.[214] In any event, regardless of which conformation of **Ag-III** (Figure 4.6) is catalytically active, the picture is invariably much more complicated than of **Ag-I** and **Ag-II**.

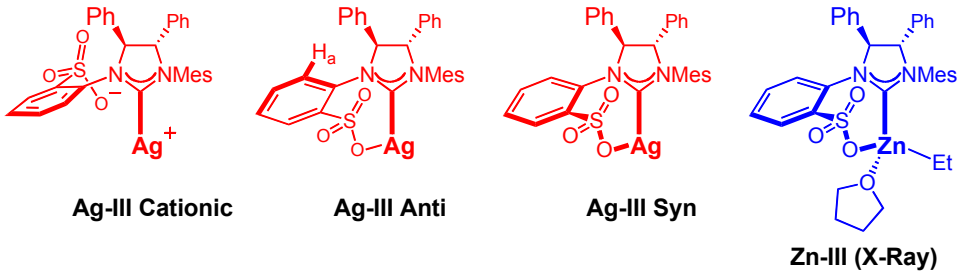


Figure 4.6: Potential Modes of Sulfonate Coordination

4.5 *Conclusions*

We have developed methods to efficiently prepare chiral NHC-based ligands bearing a sulfonate unit (**Ag-III** – **Ag-V**). Through the studies outlined above, a new method for preparation of imidazolinium salts has been discovered. We are only beginning to understand the subtle nuances of this new class of sulfonate containing NHCs (**Ag-III** – **Ag-V**) that give to rise to its superior reactivity in many reactions when phenolate-based NHC complexes (**Ag-I** and **Ag-II**) have failed.[196]

(214) Unpublished results of Yunmi Lee.

4.6 *Experimentals*

General. Infrared (IR) spectra were recorded on a Nicolet 210 spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm). High-resolution mass spectrometry were performed on a Micromass LCT ESI-MS (positive mode) at the Mass Spectrometry Facility, Boston College and at the University of Illinois Mass Spectrometry Laboratories (Urbana, Illinois). Elemental microanalyses were performed at Robertson Microlit Laboratories (Madison, NJ). Enantiomer ratios were determined by chiral GLC analysis (Alltech Associated Chiraldex GTA column (30 m x 0.25 mm) and Betadex 120 column (30 m x 0.25 mm) in comparison with authentic racemic materials. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Polarimeter.

Unless otherwise noted, all reactions were carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 ^{o}C) and flame-dried glassware with standard dry box or vacuum-line techniques. Solvents were purified under a positive pressure of dry argon by a modified Innovative Technologies purification system: toluene

and benzene were purified through a copper oxide and alumina column; CH_2Cl_2 and Et_2O were purged with argon and purified by passage through two alumina columns. Tetrahydrofuran (Aldrich) and *t*-BuOMe (Acros, 99%) were purified by distillation from sodium benzophenone ketal immediately prior to use unless otherwise specified. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Doe & Ingalls) in air.

Reagents and Catalysts:

Acetonitrile was purchased from Aldrich and used as received

Acetic acid was purchased from Fisher and used as received.

Racemic-2,2'-bis(diphenylphosphino)-1,1'-binapthyl (*rac*-binap) was purchased from Aldrich and used as received.

2-Bromomesitylene was purchased from Aldrich and used as received.

2-Bromobenzenesulfonyl chloride was purchased from Lancaster and purified by washing a benzene solution of the sulfonyl chloride with a 1.0 M aq solution of KOH (see below for details).

(*S*)-Boc-phenylglycinol can be purchased from BetaPharma or prepared[215] in one step from (*S*)-phenylglycinol (purchased from BetaPharma).

(*R*)-*tert*-Butanesulfinamide: Purchased from Advanced Asymmetrics and used as received.

(215) "Model Studies and First Synthesis of the Anitfungal and Antibacterial Agent Cladobotyal," Clive, D. L.; Huang, X. *J. Org. Chem.* **2004**, *69*, 1872-1879.

(-)-(*S,S*)-Diphenylethylenediamine (99% purity) was purchased from Astatech Inc. and used as received.

2,6-Diethylaniline was purchased from Aldrich and used as received.

1,4-Dioxane (99.0%, anhydrous) was purchased from Aldrich and used as received.

Imidazole was purchased from Aldrich and used as received.

***N*, *N*-Dimethylformamide** (99.8%, Acroseal) was purchased form Aldrich and used as received.

***N*-Methyl-*N*-methylidneiminium iodide (Eschenmoser's salt)** was purchased from Aldrich and used as received.

Palladium (II) acetate (99.9+% purity) was purchased from Aldrich and used as received.

Phenylmagnesium Bromide was prepared as a 2-3 M solution in THF from Mg(0) and bromobenzene (distillted over CaH_2 prior to use) and titrated before use.

Pyridine was purchased from Aldrich and purified by distillation over KOH before use.

pH = 7 buffer was prepared by mixing dibasic phosphate (Na_2HPO_4, 8.19 g) and monobasic phosphate (NaH_2PO_4, 5.84 g) and diluted to 1 L with distilled water.

Ruthenium (III) chloride hydrate (40-45% Ru) was purchased from Strem and used as received.

Silver (I) oxide was prepared as follows. An aqueous solution of sodium hydroxide (20 mL, 2M, 40 mmol) was added to a solution of $AgNO_3$ (1.7 g, 10 mmol) in H_2O (10 mL). A brown precipitate formed immediately, which was isolated by vacuum filtration. The

solid was washed with 250 mL H_2O, 250 mL EtOH, and 250 mL acetone and repeated. The brown solid was dried overnight under vacuum (~0.5 mm Hg) over P_2O_5.

Sodium periodate was purchased from Aldrich and used as received.

Sodium *tert*-butoxide (98%) was purchased from Strem Inc. and used as received.

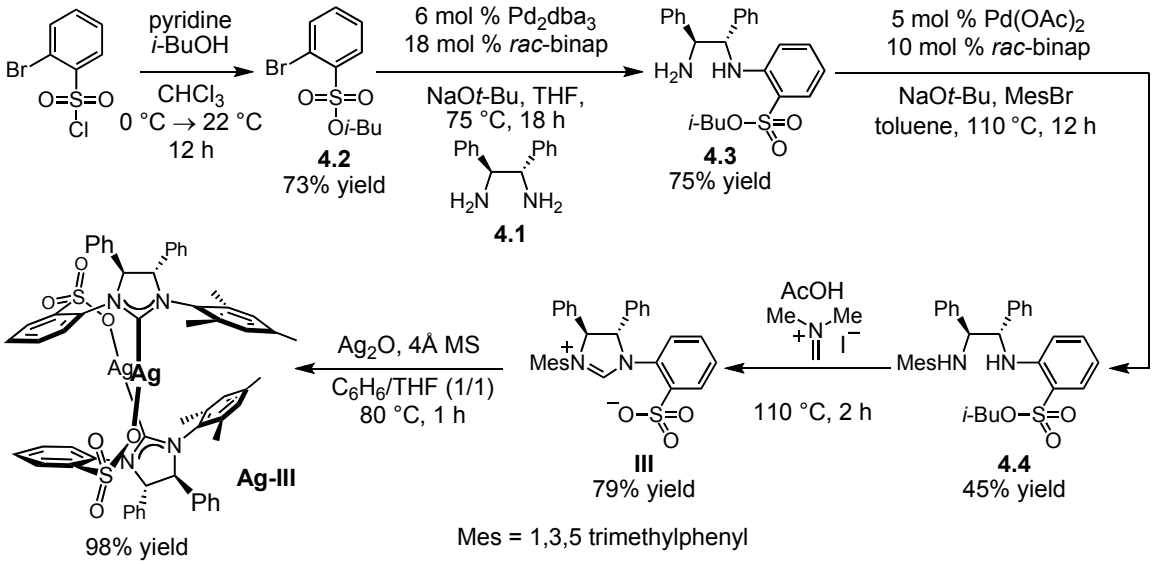
Sulfuric acid (concentrated, 18 M) was purchased from Fisher as used as received.

Thionyl chloride was purchased from Aldrich and used as received.

Triethylamine was purchased from Aldrich and distilled from CaH_2 prior to use.

Tris(dibenzylideneacetone)dipalladium (0) ($Pd_2(dba)_3$) was purchased from Strem Inc. and used as received.

■ Experimental Procedures for the Synthesis Ag-III:



Isobutyl-2-bromobenzenesulfonate (4.2). (Prior to use in this reaction, commercially available 2-bromobenzenesulfonyl chloride was dissolved in benzene and washed with a 1.0 M aq solution of KOH. The organic layer was dried with $MgSO_4$, filtered and concentrated in vacuo to afford sulfonyl chloride as a clear oil). In two separate syringes, pyridine (4.56 mL, 55.9 mmol) and a solution of 2-bromobenzenesulfonyl chloride (6.49 g, 25.4 mmol) in $CHCl_3$ (13 mL) were added dropwise at the same time over 20 min to a solution of 2-methylpropanol (2.57 mL, 27.9 mmol) dissolved in $CHCl_3$ (13 mL) at 0 ^oC under a N_2 atmosphere. The solution was allowed to stir at 22 ^oC. After 20 h, the reaction was quenched upon addition of a 0.1 M aq solution of HCl (20 mL) and allowed to stir for five minutes. The $CHCl_3$ layer was separated and washed with a 0.1 M aq solution of HCl (20 mL), water (2 × 15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to afford a clear oil, which was purified by silica gel chromatography (10% Et_2O/petroleum ether) to yield 5.42 g (18.5 mmol, 72.8%) of sulfonate ester **4.2** as a clear oil. **IR (neat):** 2964 (m), 2926 (w), 2870 (w), 1573 (w), 1455 (w), 1362 (s), 1189 (s), 965 (m), 934 (m) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.10–8.09 (1H, m, *i*-BuOSO$_2$*o*-Ar**H**), 7.78–7.56 (1H, m, Br*o*-Ar**H**), 7.50–7.44 (2H, m, *i*-BuOSO$_2$*p*-Ar**H** and *i*-BuOSO$_2$*m*-Ar**H**), 3.85 (2H, d, J = 6.6 Hz, C**H**$_2$OSO$_2$), 2.00 (1H, qt, J = 6.8, 6.6 Hz, [CH$_3$]$_2$C**H**CH$_2$), 0.93 (6H, d, J = 6.8 Hz, CH[C**H**$_3$]$_2$); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 135.9, 135.6, 134.6, 132.1, 127.6, 120.8, 77.2, 28.1, 18.7; **HRMS (EI+):** Calcd for $C_{10}H_{13}BrO_3S$: 291.9769, Found: 291.9773.

Isobutyl-2-((1*S*,2*S*)-2-amino-1,2-diphenylethylamino)benzenesulfonate (4.3). (–)-(*S*,*S*)-1,2-Diphenylethylenediamine (1.00 g, 4.71 mmol), $Pd_2(dba)_3$ (258 mg, 0.283 mmol), *rac*-binap (528 mg, 0.848 mmol) and NaO*t*-Bu (815 mg, 8.48 mmol) were weighed out into an oven-dried 250 mL round bottom flask under a N_2 atmosphere in a glove box. The flask was removed from the glove box and fitted with a reflux condenser. A solution of **4.2** (1.38 g, 4.71 mmol) dissolved in THF (47 mL) was added through a syringe and the resulting mixture was allowed to stir at reflux (~80 ^oC) (the reaction mixture becomes deep red upon heating and remains this color for the length of the reaction). After 15 h, the mixture was allowed to cool to 22 ^oC and the volatiles were removed in vacuo affording a deep red oil. The deep red oil was then dissolved in toluene, loaded on top of a column containing silica gel, and purified by silica gel chromatography (100% petroleum ether (to elute toluene) to 50% Et_2O/petroleum ether) to afford 1.50 g (3.53 mmol, 74.9%) of **4.3** as a yellow solid. **mp:** 157-159 ^oC; **IR (neat):** 3364 (br), 2966 (w), 2874 (w), 1601 (m), 1504 (m), 1461 (m), 1167 (m), 978 (m) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.67 (1H, dd, *J* = 8.1, 1.7 Hz, *i*-BuOSO$_2$*o*-Ar**H**), 7.49 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.44 (1H, d, *J* = 7.0 Hz, N**H**) 7.35–7.22 (8H, m, Ar**H**), 7.13 (1H, dd, *J* = 8.1, 7.2 Hz, *i*-BuOSO$_2$*p*-Ar**H**), 6.57 (1H, dd, *J* = 8.1, 7.2 Hz, *i*-BuOSO$_2$*m*-Ar**H**), 6.31 (1H, d, *J* = 8.1 Hz, *i*-BuOSO$_2$*m*-Ar**H**), 4.59 (1H, dd, *J* = 7.0, 3.5 Hz, NHC**H**), 4.40 (1H, d, *J* = 3.5 Hz, NHC**H**), 3.74 (1H, dd, *J* = 9.3, 6.8 Hz, C**H**HOSO$_2$), 3.70 (1H, dd, *J* = 9.3, 6.6 Hz, CH**H**OSO$_2$), 1.95 (1H, ddqq, *J* = 6.8, 6.8, 6.8, 6.6 Hz, [CH$_3$]$_2$C**H**CH$_2$), 1.51 (2H, br, N**H**), 0.92 (3H, d, *J* = 6.8 Hz, CH[C**H**$_3$]$_2$), 0.85 (3H, d, *J* = 6.8 Hz, CH[C**H**$_3$]$_2$); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 145.8, 142.6, 140.7, 135.1, 130.8,

128.8, 128.4, 127.6, 127.6, 127.1, 126.8, 116.5, 115.1, 113.6, 76.3, 63.0, 61.2, 28.1, 18.8, 18.7; **HRMS (EI+):** Calcd for $C_{24}H_{29}N_2O_3S$: 425.1899 (M^++H), Found 425.1895; **Optical Rotation:** $[\alpha]_D^{25}$ –98.9 (*c* 1.00, $CHCl_3$).

Isobutyl-2-((1*S*,2*S*)-2-(mesitylamino)-1,2-diphenylethylamino)benzenesulfonate (4.4). Diamine **4.3** (0.800 g, 1.88 mmol), $Pd(OAc)_2$ (42.0 mg, 0.188 mmol), *rac*-binap (234 mg, 0.376 mmol) and NaO*t*-Bu (272 mg, 2.83 mmol) were weighed out into an oven-dried 50 mL round bottom flask under a N_2 atmosphere in a glove box. The flask was removed from the glove box and fitted with a reflux condenser. A solution of 2-bromomesitylene (577 μL, 3.77 mmol) dissolved in toluene (19 mL) was added through a syringe and the resulting mixture was allowed to stir at 110 °C (the mixture becomes deep red upon heating and remains this color for the length of the reaction). After 18 h, the mixture was allowed to cool to 22 °C, loaded directly on top of a column containing silica gel and purified by silica gel column chromatography (100% petroleum ether (to elute toluene) to 20% Et_2O/petroleum ether) to afford a pale yellow solid, which was rinsed with petroleum ether to yield 441 mg (0.811 mmol, 43.1%) of diamine **4.4** as a white solid. **mp:** 164-166 °C; **IR (neat):** 3352 (m), 2962 (m), 2917 (w), 2861 (w), 1596 (s), 1350 (s) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.82 (1H, dd, *J* = 8.1, 1.7 Hz, *i*-$BuOSO_2$*o*-Ar**H**), 7.42 (1H, d, *J* = 4.5 Hz, N**H**), 7.30–7.12 (9H, m, *i*-$BuOSO_2$*p*-Ar**H** and Ar**H**), 7.07–7.04 (2H, m, Ar**H**), 6.75–6.72 (3H, m, *i*-$BuOSO_2$*m*-Ar**H** and Mes**H**), 6.57 (1H, d, *J* = 8.4 Hz, *i*-$BuOSO_2$*m*-Ar**H**), 4.97 (1H, dd, *J* = 7.0, 4.5 Hz, NHC**H**), 4.57 (1H, d, *J* = 7.0 Hz, NHC**H**), 3.88 (1H, dd, *J* = 9.3, 6.6 Hz, C**H**$HOSO_2$), 3.78 (1H, dd, *J* = 9.3,

6.4 Hz, CH**H**OSO_2), 3.65 (1H, br s, N**H**), 2.20 (3H, s, C**H**$_3$Ar), 2.15 (6H, s, C**H**$_3$Ar), 2.01 (1H, ddqq, J = 6.6, 6.4, 4.2, 4.0 Hz, $[CH_3]_2$C**H**CH_2), 0.99 (3H, d, J = 4.0 Hz, CH[C**H**$_3]_2$), 0.97 (3H, d, J = 4.2 Hz, CH[C**H**$_3]_2$); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 145.7, 140.9, 140.2, 140.1, 135.1, 131.1, 130.9, 129.8, 129.2, 128.4, 128.2, 128.1, 127.8, 127.6, 117.6, 115.8, 113.9, 76.2, 66.7, 62.0, 28.2, 20.5, 19.2, 18.8; **HRMS (EI+):** Calcd for $C_{33}H_{39}N_2O_3S$: 543.2681 (M^++1), Found 543.2680; **Optical Rotation:** $[\alpha]_D^{25}$ –94.4 (*c* 0.100, $CHCl_3$).

Imidazolium Salt E. Diamine **4.4** (1.56 g, 2.87 mmol) and Eschenmoser's salt (2.60 g, 14.3 mmol) were weighed out into a screw cap vial (2 x 8 cm), which was sealed with a septum and purged with N_2. Acetic acid (2.48 mL, 43.0 mmol) was added through a syringe. The vial was sealed with a screw cap and allowed to stir at 110 ^oC (the heterogeneous mixture becomes yellow then black and homogeneous upon heating). After 2 h, the mixture was allowed to cool to 22 ^oC and diluted with Et_2O (5 mL) and water (5 mL). The reaction was neutralized by the *slow* addition of a saturated aqueous solution of K_2CO_3 until gas evolution ceased. Dichloromethane (10 mL) was added and the aqueous layer separated. The aqueous layer was washed with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a yellow solid. The yellow solid was purified by silica gel column chromatography (100% CH_2Cl_2 to 0.5% MeOH/CH_2Cl_2 to 1.0% MeOH/CH_2Cl_2) to afford 1.12 g (2.26 mmol, 79.0%) of imidazolium salt **III** as a white solid. (Note: Separation of a yellow impurity by silica gel column chromatography can often be

tedious. Precipitation of **III** from a CH_2Cl_2 solution with petroleum ether can remove trace amounts of this yellow impurity after careful silica gel column chromatography. This material was obtained in crystalline form by recrystallization from CH_2Cl_2:Et_2O, but recrystallization is not required for effective formation of **Ag-III**.) **mp:** 223-225 ^oC; **IR (neat):** 3058 (m), 2914 (m), 2861 (w), 1623 (s), 1579 (m), 1230 (s) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.72 (1H, s, NC**H**N), 8.23 (1H, dd, *J* = 7.9, 1.5 Hz, SO_2*o*-Ar**H**), 7.67–7.64 (2H, m, Ar**H**), 7.50–7.47 (2H, m, Ar**H**), 7.43–7.41 (3H, m, Ar**H**), 7.36–7.30 (4H, m, SO_2*m*-Ar**H** and Ar**H**), 7.10 (1H, td, *J* = 7.9, 1.5 Hz, SO_2*p*-Ar**H**), 6.93 (1H, s, Mes**H**), 6.73 (1H, s, Mes**H**), 6.72 (1H, dd, *J* = 7.9, 1.5 Hz, SO_2*m*-Ar**H**), 6.56 (1H, d, *J* = 11.8 Hz, NC**H**), 5.53 (1H, d, *J* = 11.8 Hz, NC**H**), 2.60 (3H, s, C**H**$_3$Ar), 2.23 (3H, s, C**H**$_3$Ar), 2.00 (3H, s, C**H**$_3$Ar); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 158.7, 144.0, 140.4, 138.6, 135.0, 134.3, 131.5, 130.7, 130.5, 130.5, 130.3, 130.0, 129.9, 129.7, 129.6, 129.1, 129.1, 127.5, 76.2, 74.5, 21.0, 18.8, 18.5; **HRMS (EI+):** Calcd for $C_{30}H_{29}N_2O_3S$: 497.1899 (M^++H), Found 497.1886; **Elemental Analysis:** Anal Calcd for $C_{30}H_{28}N_2O_3S$: C 72.55; H 5.68; N 5.64; Found C 72.27; H 5.41; N 5.45; **Optical Rotation:** $[\alpha]_D^{25}$ –14.9 (*c* 0.500, $CHCl_3$).

Ag-III. Imidazolium salt **III** (100 mg, 0.201 mmol), Ag_2O (93.0 mg, 0.400 mmol) and oven-dried powdered <5 micron 4Å MS (ca. 50 mg) were weighed out into an oven-dried 10 mL round bottom flask. The flask was purged with N_2, fitted with a reflux condenser, and wrapped with aluminum foil to exclude light. Tetrahydrofuran (1.0 mL) followed immediately by benzene (1.0 mL) were added through a syringe resulting in a black

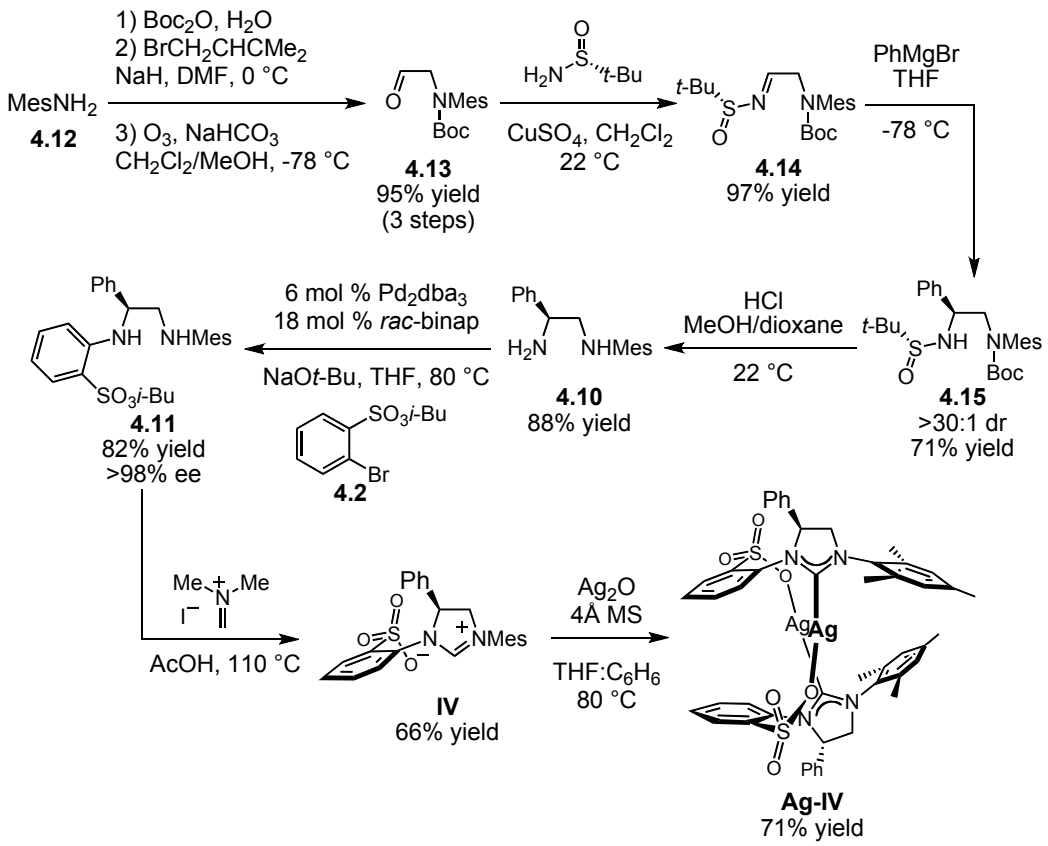
heterogeneous mixture. The mixture was allowed to stir at 80 °C. After 1 h, the mixture was allowed to cool to 22 °C and filtered through a short plug of Celite 545 (4 x 1 cm) eluted with THF (ca. 20 mL). The solution was concentrated in vacuo to afford 119 mg (0.197 mmol, 98.0%) of **Ag-III** as a white solid, which was stored under low light conditions. (Note: This material was obtained in crystalline form by recrystallization from CH_2Cl_2:Et_2O bilayer, but recrystallization is not required for effective Cu-catalyzed ACA). **mp:** 247-249 °C (dec.); **IR (neat):** 3062 (w), 3026 (w), 2908 (w), 1608 (w), 1480 (s), 1455 (s), 1226 (s), 1201 (s), 1027 (m), 754 (s) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.27 (1H, br d, *J* = 7.3 Hz, Ar**H**), 7.50–7.44 (2H, m, Ar**H**), 7.32–6.95 (9H, m, Ar**H**), 6.80 (2H, br s, Ar**H**), 6.55 (1H, br d, *J* = 10.4 Hz, NC**H**), 6.33 (2H, br s, Ar**H**), 5.18 (1H, br d, *J* = 10.4 Hz, NC**H**), 2.46 (3H, s, C**H**$_3$Ar), 2.29 (3H, s, C**H**$_3$Ar), 1.42 (3H, s, C**H**$_3$Ar); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 205.6 ($J_{C^{109}Ag}$ = 186.8 Hz, $J_{C^{107}Ag}$ = 182.5 Hz), 143.4, 138.6, 138.5, 136.5, 135.7, 135.2, 134.1, 131.1, 130.6, 130.0, 129.9, 129.6, 128.9, 128.8, 128.6, 128.5, 128.4, 128.2, 76.5, 74.0, 68.6, 21.1, 19.0, 17.9; **Optical Rotation:** $[\alpha]_D^{25}$ –104 (*c* 0.500, $CHCl_3$).

Aminal 4.5. IR (neat): 2971 (m), 2925 (m), 2868 (m), 1594 (w), 1478 (s), 1357 (m), 1282 (w), 1184 (s), 977 (m), 942 (m), 907 (m), 856 (w), 729 (w), 700 (m), 602 (m) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.90 (1H, dd, *J* = 8.4, 1.6 Hz) 7.32 (1H, ddd, *J* = 8.8, 7.2, 1.6 Hz) 7.23-7.15 (10H, m), 7.07 (1H, d, *J* = 8.4 H), 6.94 (1H, t, *J* = 8.0 Hz), 6.69 (2H, br s), 5.45 (1H, d, *J* = 4.4 Hz), 4.88 (2H, q, *J* = 8.0 Hz), 4.65 (1H, d, *J* = 4.4 Hz), 3.90 (1H, dd, *J* = 9.2, 6.0 Hz), 3.78 (1H, dd, *J* = 9.2, 6.8 Hz), 2.43 (3H, br s), 2.32 (3H, br

s), 2.14 (3H, s), 1.99 (1H, sep, J = 6.4 Hz), 0.89 (3H, d, J = 5.6 Hz), 0.88 (3H, d, J = 5.6 Hz); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 147.2, 138.3, 138.2, 138.1 (br), 137.7, 136.6 (br), 135.3, 14.1, 132.0, 130.9 (br), 129.1 (br), 128.5, 128.5, 128.2, 128.0, 127.7, 126.7, 120.5, 120.2, 76.4, 74.2, 73.8, 73.7, 28.2, 20.8, 20.6 (br), 19.2 (br), 18.9, 17.8; **HRMS (ESI+):** Calcd for $C_{34}H_{39}N_2O_3S$: 555.26814 (M^++H), Found 555.26798.

N-Me product 4.6. IR (neat): 3338 (bs w), 2973 (m), 2929 (m), 2854 (w), 1607 (s), 1576 (m), 1500 (s), 1469 (s), 1355 (s), 1293 (w), 1186 (s), 984 (m), 934 (m), 852 (m), 814 (m), 757 (m), 707 (m), 594 (m) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.72 (1H, dd, J = 8.0, 1.6 Hz), 7.24-7.16 (4H, m), 7.12-7.02 (5H, m), 6.86-6.80 (3H, m), 6.67-6.61 (2H, m), 6.46 (1H, d, J = 8.4 Hz), 4.92 (1H, dd, J = 6.8, 5.2 Hz), 4.53 (1H, d, J = 6.8 Hz), 3.81 (1H, dd, J = 9.2, 6.4 Hz), 3.63 (1H, dd, J = 9.2, 6.4 Hz), 2.71 (3H, s), 2.41 (3H, s), 2.23 (3H, s), 1.94 (1H, sep, J = 6.8 Hz), 1.76 (3H, s), 0.94 (3H, d, J = 4.0 Hz), 0.92 (3H, d, J = 4.0 Hz); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 145.9, 144.8, 140.0, 137.3, 137.1, 137.0, 135.2, 134.6, 131.0, 130.6, 130.1, 129.8, 128.4, 127.9, 127.8, 127.7, 127.2, 117.1, 115.6, 113.7, 76.3, 72.9, 58.5, 38.0, 28.2, 20.8, 20.5, 20.0, 19.0, 18.8; **HRMS (ESI+):** Calcd for $C_{34}H_{41}N_2O_3S$: 557.28379 (M^++H), Found 557.28161.

■ Experimental Procedures for 1st Generation Synthesis of Ag-IV

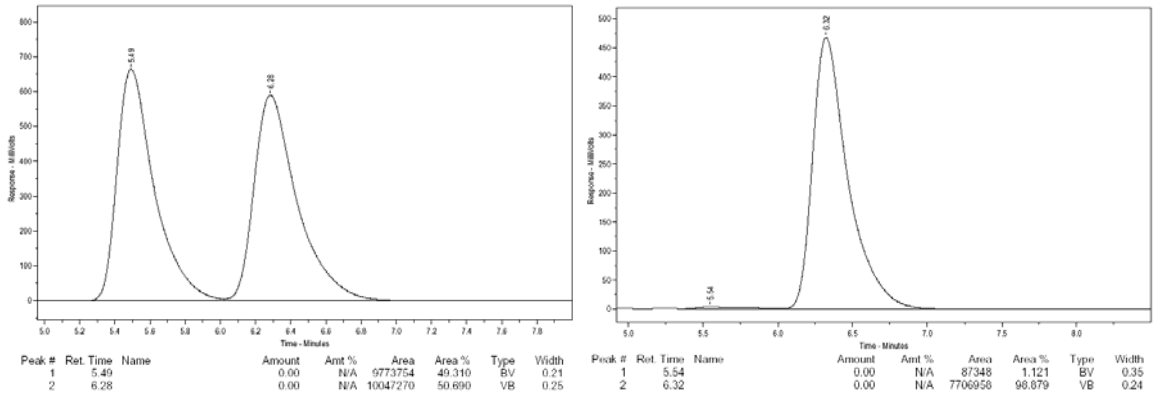


(*R*)-*tert*-Butyl 2-(*tert*-butylsulfinylimino)ethyl(mesityl)carbamate (4.14). Copper(II) sulfate (1.59 g, 10.0 mmol) was added to a solution of (*R*)-*tert*-butanesulfinamide (533 mg, 4.40 mmol) and aldehyde **4.13**[194a] **(**1.10 g, 4.0 mmol) dissolved in CH_2Cl_2 (8.00 mL). The mixture was allowed to stir at 22 °C for 24 h. At this time the mixture was passed through a short plug of silica gel (5 cm x 5 cm) eluted with EtOAc (200 mL). The volatiles were removed in vacuo affording 1.52 g (4.00 mmol, >98.0%) of sulfinylimine **4.14** as a clear oil. This material was carried on directly to next reaction.

***tert*-Butyl (*S*)-2-((*R*)-1,1-dimethylethylsulfinamido)-2-phenylethyl(mesityl)carbamate (4.15).** To a flame-dried 100 mL round bottom flask was charged with sulfinylimine **4.14** (1.52 g, 4.00 mmol). Tetrahydrofuran (35 mL) was added and the solution was allowed to cool to –78 °C (dry ice/acetone). Phenylmagnesium bromide (2.30 M in Et_2O, 4.00 mL, 9.20 mmol) was added dropwise over 10 min and the mixture allowed to stir for 15 h. At this time the reaction was quenched through the addition of a saturated aqueous solution of ammonium chloride (40 mL) and allowed to warm to 22 °C. The mixture was extracted with EtOAc (3 x 40 mL) and the combined organic layers dried over $MgSO_4$, filtered and concentrated to afford yellow oil. The oil was purified by silica gel column chromatography (5% EtOAc/petroleum ether to 50% EtOAc/petroleum ether) to afford 1.30 g of **4.15** (2.83 mmol, 70.7%, >98:2 dr) as a clear oil. **IR (neat):** 3257 (b), 3029 (w), 2978 (s), 2923 (s), 2873 (m), 1687 (s), 1476 (m), 1450 (m), 1387 (s), 1366 (s), 1311 (s), 1256 (w), 1168 (s), 1151 (s), 1071 (s), 995 (w), 927 (m), 847 (m), 733 (m), 699 (m), 644 (w) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ (85:15 mixture of rotamers) 7.31-7.21 (5H, m), 6.90 (1H, s), 6.82 (1H, s), 6.77 (1H, s), 5.00 (1H, d, *J* = 7.6 Hz), 4.56 (1H, q, *J* = 6.8 Hz), 4.46 (1H, ddd, *J* = 10.4, 8.0, 4.4 Hz), 4.34 (1H, dd, *J* = 14.4, 10.4 Hz), 4.14-4.08 (1H, m), 3.58-3.45 (2H, m), 3.04 (1H, dd, *J* = 14.4, 4.4 Hz), 2.27 (3H, s), 2.34 (3H, s), 2.22 (3H, s), 2.06 (3H, s), 1.98 (3H, s), 1.88 (3H, s), 1.80 (3H, s), 1.54 (9H, s), 1.32 (9H, s), 1.23 (9H, s), 1.20 (9H, s); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 156.5, 154.2, 140.8, 140.3, 138.2, 137.3, 136.7, 135.7, 135.0, 134.5, 129.5, 129.3, 128.9, 128.7, 128.5, 128.2, 127.9, 127.8, 127.5, 80.8, 80.0, 61.3, 59.1, 56.4, 56.2, 56.0, 55.8, 28.5, 28.2, 22.7, 22.6,

20.9, 18.6, 18.3, 17.9 ; **HRMS (EI+):** Calcd for $C_{26}H_{38}N_2O_3S$: 459.2681 (M^++H), Found 459.2683.

Enantiomeric purity was determined by chiral HPLC analysis in comparison with authentic racemic material (98% ee shown; chiralpak OD column (25 cm x 0.46 cm), 90/10 hexanes/*i*-PrOH, 1.0 mL/min, 254 nm).



(*S*)-*N*-Mesityl-2-phenylethane-1,2-diamine (4.10). A 50 mL round bottom flask was charged with sulfinamide **4.15** (5.23 g, 11.4 mmol). Methanol (38 mL) was added and the solution was allowed to cool to –78 °C. To this solution was added HCl (4.00 M in dioxane, 28.5 mL, 114 mmol) and the resulting solution allowed to warm to 22 °C and stir for 4 h. The reaction was quenched through the addition of a saturated aqueous solution of sodium bicarbonate and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a yellow oil,

which was purified by silica gel chromatography (50% EtOAc/petroleum ether) to deliver 2.74 g of **4.10** (10.7 mmol 94.4%) as a yellow oil. **IR (neat):** 3368 (bs), 3059 (m), 3025 (m), 2918 (bs), 2854 (m), 2725 (w), 1601 (m), 1484 (s), 1451 (s), 1374 (m), 1303 (m), 1265 (s), 1232 (s), 1154 (m), 1026 (m), 855 (m), 740 (s), 702 (s) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.38 (1H, s), 7.37 (3H, s), 7.29 (1H, s, *J* = 4.4 Hz), 6.81 (2H, s), 4.11 (1H, *J* = 7.6, 5.2 Hz), 3.18 (1H, dd, *J* = 12.0, 5.2 Hz), 3.08 (1H, dd, *J*= 12.0, 8.0 Hz), 2.30 (2H, bs), 2.23 (3H, s), 2.20 (6H, s); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 144.3, 143.2, 131.2, 129.6, 129.4, 128.6, 127.3, 126.3, 56.3, 56.0, 20.5, 18.2; **HRMS (EI+):** Calcd for $C_{17}H_{23}N_2$: 255.1861 (M^++H), Found 255.1869; **Optical Rotation:** $[\alpha]_D^{25}$ +11.3 (*c* 2.03, $CHCl_3$).

(*S*)-Isobutyl 2-(2-(mesitylamino)-1-phenylethylamino)benzenesulfonate (4.11). Tris(dibenzylideneacetone) dipalladium(0) (591 mg, 0.646 mmol), *rac*-binap (1.21 mg, 1.94 mmol) and NaO*t*-Bu (1.86 mg, 19.4 mmol) were weighed into an oven-dried 250 mL round bottom flask under a N_2 atmosphere in a glove box. The flask was sealed with a septum, removed from the glove box and fitted with a reflux condenser. A solution of aryl bromide **4.2** (3.16 g, 10.8 mmol) and diamine **4.10** (2.74 g, 10.8 mmol) dissolved in THF (70 mL) was added through a syringe and the resulting mixture was allowed to stir at reflux (~80 °C) (the reaction mixture becomes deep red upon heating and remains this color for the length of the reaction). After 36 h, the mixture was allowed to cool to 22 °C and the mixture filtered through a short plug of celite (10 cm x 5 cm) eluted with CH_2Cl_2 (100 mL). The volatiles were removed in vacuo to afford a deep red oil, which was

purified by silica gel chromatography (10% Et_2O/petroleum ether) to afford 3.32 g (7.12 mmol, 66.1%) of **4.11** as a yellow semi-solid. **IR (neat):** 3371 (w), 2966 (m), 2923 (w), 2868 (w), 1733 (w), 1602 (m), 1573 (w), 1509 (w), 1484 (m), 1467 (s), 1450 (m), 1349 (s), 1298 (w), 1180 (s), 1163 (s), 1121 (w), 1092 (w), 978 (m), 940 (m), 910 (w), 847 (w), 817 (w), 746 (s), 699 (m) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.75 (1H, dd, *J* = 8.0, 1.6 Hz), 7.39-7.33 (4H, m), 7.30-7.23 (2H, m), 6.97 (1H, d, *J* = 6.4 Hz), 6.69 (2H, s), 6.68 (1H, dt, *J* = 7.2, 0.8 Hz), 6.51 (1H, d, *J* = 8.4 Hz), 4.70 (1H, ddd, *J* = 6.4, 6.4, 4.4 Hz), 3.83 (1H, dd, *J* = 9.2, 6.4 Hz), 3.78 (1H, dd, *J* = 9.2, 6.4 Hz), 3.35 (1H, dd, *J* = 12.0, 4.0 Hz), 3.20 (1H, dd, *J* = 12.4, 6.4 Hz), 3.02 (1H, bs), 2.21 (3H, s), 2.12 (6H, s), 1.97 (1H, sep, *J* = 6.4 Hz), 0.94 (3H, d, *J* = 2.8 Hz), 0.92 (3H, d, *J* = 3.2 Hz); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 145.8, 142.1, 140.1, 135.2, 132.1, 130.8, 130.6, 129.4, 128.9, 127.7, 126.3, 116.8, 115.6, 113.6, 76.2, 57.2, 54.6, 28.0, 20.6, 186, 17.8; **HRMS (EI+):** Calcd for $C_{27}H_{34}N_2O_3SNa$: 489.2188 (M^++Na), Found 489.2183; **Optical Rotation:** $[\alpha]_D^{25}$ –43.0 (*c* 2.28, $CHCl_3$).

Imidazolinium Salt IV. Diamine **4.11** (521 mg, 1.11 mmol) and Eschenmoser's salt (1.02 g, 5.55 mmol) was weighed into a screw cap vial (2 x 8 cm), which was sealed with a septum and purged with N_2. Acetic acid (958 μL, 16.6 mmol) was added through a syringe. The vial was sealed with a screw cap and allowed to stir at 110 °C (the heterogeneous mixture becomes yellow then black and homogeneous upon heating). After 30 minutes, the mixture was allowed to cool to 22 °C and diluted with Et_2O (5 mL) and water (5 mL). The reaction was neutralized by the *slow* addition of a saturated

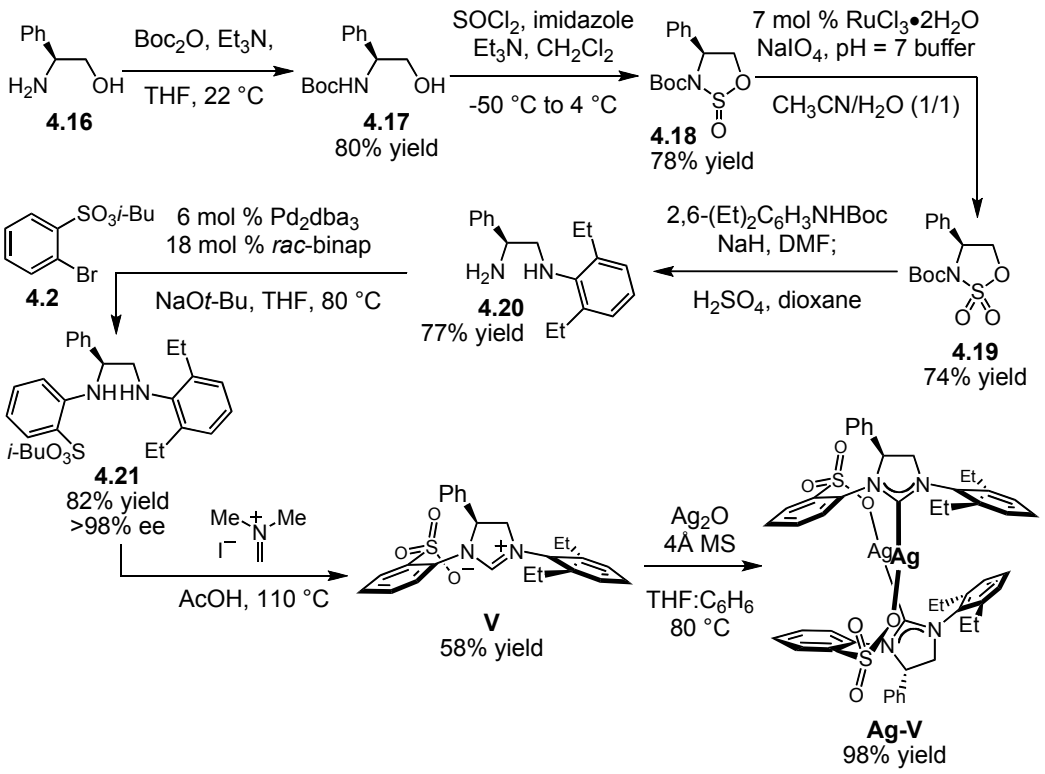
aqueous solution of K_2CO_3 until gas evolution ceased. Dichloromethane (20 mL) was added and the aqueous layer separated. The aqueous layer was washed with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a yellow solid. The yellow solid was purified by silica gel column chromatography (100% CH_2Cl_2 → 1.0% MeOH/CH_2Cl_2 → 2.0% MeOH/CH_2Cl_2) to afford 373 mg (0.888 mmol, 80.0%) of imidazolinium salt **IV** as a white solid. (Note: Separation of a yellow colored impurity by silica gel column chromatography can often be tedious. Precipitation of **IV** from a CH_2Cl_2 solution with petroleum ether can remove trace amounts of this yellow impurity after careful silica gel column chromatography. **mp:** 189-191 °C; **IR (neat):** 3447 (b), 1636 (s), 1471 (w), 1244 (m), 1197 (m), 1142 (w), 1101 (w), 1087 (w), 860 (w) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.93 (1H, s), 7.92 (1H, dd, *J* = 7.6, 1.2 Hz), 7.46-7.45 (2H, m), 7.37-7.30 (3H, m), 7.10 (1H, dt, *J* = 6.4, 1.2 Hz), 6.94 (1H, dt, *J* = 8.0, 1.6 Hz), 6.90 (1H, bs), 6.86 (1H, bs), 6.71 (1H, dd, *J* = 7.6, 0.8 Hz), 6.26 (1H, dd, *J* = 12.4, 9.2 Hz), 7.74 (1H, t, 12.4 Hz), 3.98 (1H, dd, *J* = 11.6, 9.6 Hz), 2.43 (3H, bs), 2.89 (6H, bs); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 160.4, 143.3, 140.4, 136.9, 136.5, 135.3, 130.9, 130.5, 130.3, 130.0, 129.8, 129.4, 129.4, 128.5, 127.1, 68.0, 59.0, 21.3, 18.4, 18.0; **HRMS (EI+):** Calcd for $C_{24}H_{24}N_2O_3SNa$: 443.1405 (M^++Na), Found 443.1398; **Optical Rotation:** $[\alpha]_D^{25}$ +144 (*c* 1.00, $CHCl_3$).

Ag-IV. Imidazolinium salt **IV** (50.0 mg, 0.119 mmol), Ag_2O (109 mg, 0.476 mmol) and oven-dried powdered <5 micron 4Å MS (ca. 50 mg) were weighed out into an oven-dried

2 x 8 cm vial wrapped with aluminum foil to exclude light. The vial was sealed with a septum, purged with N_2 and Tetrahydrofuran (1.5 mL) followed immediately by benzene (1.5 mL) were added through a syringe, which resulted in a black heterogeneous mixture. The vial was sealed with a screw cap and the mixture was allowed to stir at 80 °C. After 1.5 h, the mixture was allowed to cool to 22 °C and filtered through a short plug of Celite 545 (4 x 1 cm) eluted with THF (ca. 20 mL). The solution was then concentrated in vacuo to afford 45 mg (0.0850 mmol, 71.4%) of **Ag-IV** as a white solid, which was stored under low light conditions. **mp:** 240 °C (dec.); **IR (neat):** 3468 (b), 3067 (w), 3033 (w), 2944 (w), 2923 (w), 1640 (m), 1607 (m), 1590 (m), 1569 (m), 1484 (s), 1438 (s), 1265 (s), 1210 (s), 1142 (m), 1092 (m), 1024 (s), 1007 (w), 902 (m), 847 (m), 771 (m), 729 (s), 699 (s), 611 (m), 564 (m), 522 (w) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.09 (1H, br s), 7.26-7.10 (6H, br m), 6.80 (1H, br s), 6.71 (1H, br s), 6.57 (1H, bs s), 6.31 (1H, br s), 6.16 (1H, br s), 4.36-4.29 (1H, br m), 3.65 (1H, br s), 2.30 (3H, s), 2.24 (3H, s), 1.94 (3H, s); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 206.5 ($C_{carbene}$, d, J = 185.5 Hz), 143.3, 139.9, 137.4, 137.2, 135.8, 135.5, 135.1, 130.7, 130.2, 129.5, 129.0, 128.6, 128.4, 128.3, 68.1, 60.2, 21.4, 18.8, 18.0; **Optical Rotation:** $[\alpha]_D^{25}$ 70.1 (*c* 0.727, $CHCl_3$).

■ **Experimental Procedures for the 2nd Generation Synthesis Ag-IV:**

(The procedures outlined below are for a related Ag-NHC complex bearing a 2,6-diethylaryl unit vs. a mesityl group. The synthesis of each Ag-NHC complex is identical.)



(*S*)-Sulfamidate (4.19): To a solution of imidazole (4.54 g, 66.2 mmol), Et_3N (7.48 mL, 45.8 mmol) and $SOCl_2$ (1.62 mL, 22.3 mmol) in CH_2Cl_2 (170 mL) at -50 °C (dry ice/acetone bath) was added (*S*)-Boc-phenylglycinol (**4.17**) (3.96 g, 16.8 mmol) as a CH_2Cl_2 solution (43.8 mL) over 1.5 h through an addition funnel. The solution was allowed to warm to 4 °C (cold room) and stir for 12 h. The reaction was quenched through the addition of water (100 mL). The organic layer was separated and the aqueous layer washed with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford **4.18** as a white solid (3.67 g, 13.1 mmol, 78.4%).

Sulfamidite **4.18** (3.67 g, 13.1 mmol) and $RuCl_3 \bullet 2H_2O$ (0.190 g, 0.914 mmol) were dissolved in CH_2Cl_2 (26.1 mL) and CH_3CN (26.1 mL) and the resulting solution was allowed to cool to 0 °C (ice bath). After 10 minutes, $NaIO_4$ (4.47 g, 20.9 mmol) and pH = 7 buffer (26.1 mL, 0.1 M aqueous solution of a 1:1 solution of Na_2HPO_4:NaH_2PO_4)[216] was added. The solution was allowed to stir at 0 °C for 20 min before allowing to warm to 22 °C over 5 min. The solution was filtered through a plug of Celite 545 (4 x 4 cm) eluted with CH_2Cl_2 (200 mL). The filtrate was diluted with water (100 mL) and the layers separated. The aqueous layer was washed with CH_2Cl_2 (2 x 100 mL) and the combined organic layers were washed with brine (1 x 100 mL), dried over $MgSO_4$, filtered and concentrated. The solid was filtered through silica gel (4 x 4 cm) eluted with CH_2Cl_2 to afford **4.19** as a white solid (2.90 g, 9.69 mmol, 74.2 %). **m.p.:**; 144-150 °C **IR (neat)**: 2976 (w), 1723 (s), 1458 (w), 1368 (s), 1320 (s), 1309 (w), 1259 (w), 1227 (w), 1190 (s), 1150 (s), 1031 (w), 1006 (w), 996 (m), 959 (w), 927 (m), 851 (s), 834 (s), 797 (m), 779 (m), 763 (s), 723 (s), 704 (m), 661 (s), 604 (s), 574 (w), 528 (w), 498 (w), 456 (w) cm^{-1}; **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.45-7.35 (5H, m), 5.29 (1H, q, *J* = 4.4 Hz), 4.87 (1H, dd, *J* = 9.2, 8.0 Hz), 4.39 (1H, dd, *J* = 9.2, 4.0 Hz), 1.42 (9H, s); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 148.4, 137.0, 129.3, 129.2, 126.2, 85.6, 71.9, 60.8, 27.9; **Optical Rotation:** $[\alpha]_D^{20}$ –45.6 (*c* 1.17, $CHCl_3$)

***tert*-Butyl-2,6-diethylphenylcarbamate:** To a solution of 2,6-diethylaniline (9.10 g, 61.0 mmol) in water (61.0 mL) was added $(Boc)_2O$ (14.8 g, 67.8 mmol) in one portion.

(216) The type of pH = 7 buffer used was found to be critical in order to achieve complete conversion in 30 min.

After 48 h, a red semi-solid precipitated out of solution. The red solid was collected by vacuum filtration, washed with water (3 x 100 mL) and dried in a vacuum desiccators over P_2O_5 for 12 h to yield a light red solid (13.7 g, 54.9 mmol, 89.9%). **m.p.:** 55-57 °C; **IR (neat)**: 3296 (br), 2965 (m), 2932 (m), 2873 (w), 1687 (s), 1618 (w), 1591 (w), 1505 (s), 1458 (w), 1390 (m), 1364 (m), 1268 (m), 1244 (w), 1164 (m), 1054 (m), 1024 (m), 916 (w), 867 (w), 840 (w), 805 (w), 776 (w), 755 (w), 720 (w), 612 (w), 564 (w), 538 (m), 492 (w), 455 (w), 404 (w) cm^{-1}; This compound is isolated as a mixture of rotomers. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.23-7.09 (3H, m), 5.84 (1H, br s), 5.58 (0.2H, br s), 2.64 (4H, q, *J* = 7.6 Hz), 1.51 (9H, br s), 1.38 (0.3H, br s), 1.20 (6H, t, *J* = 7.6 Hz); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 154.6, 143.3, 133.0, 127.8, 126.5, 126.2, 118.5, 79.9, 28.6, 25.0, 24.5, 14.7, 13.3; **HRMS (EI+):** Calcd for $C_{15}H_{27}N_2O_2$ $[M^+ + NH_4]$: 267.20725, Found: 267.20686.

(*S*)-*N*-(2,6-Diethylphenyl)-2-phenylethane-1,2-diamine (4.20): To a flame-dried flask was added NaH (60% dispersion in oil, 215 mg, 5.39 mmol) and DMF (11.0 mL). *tert*-Butyl-2,6-diethylphenylcarbamate (1.19 g, 4.76 mmol) was added as a solid in one portion and the solution was allowed to stir until it turned clear (~15 min) at 22 °C. At this time, sulfonamide **4.19** (0.951 g, 3.17 mmol) was added as a solid in one portion and the resulting mixture was allowed to stir for 12 h. Dimethylformamide was removed under reduced pressure (~0.5 mm/Hg) with gentle heating (<60 °C). Dioxane (11.0 mL) was added followed by concentrated H_2SO_4 (0.480 mL, ~18 M). The solution was allowed to stir for 30 minutes before another portion of concentrated H_2SO_4 (1.90 mL,

~18 M) was added to the solution. The resulting solution was allowed to stir at 22 °C for 48 h. A saturated aqueous solution of Na_2CO_3 was then added until pH = ~10; CH_2Cl_2 (100 mL) was added and the organic layer separated. The aqueous layer was washed with CH_2Cl_2 (100 mL x 3) and the organic layers were combined, dried over Mg_2SO_4, filtered and concentrated under reduced pressure to afford a light yellow oil. The oil was passed through a short plug of silica gel (1:1 petroleum ether/Et_2O to 3:1 petroleum ether/Et_2O) to afford **4.20** (0.659 g, 2.46 mmol, 77.3%) as a yellow oil. **IR (neat)**: 3363 (br), 3059 (w), 3033 (w), 2957 (s), 2932 (m), 2868 (m), 2366 (w), 2341 (w), 1733 (m), 1704 (w), 1594 (m), 1488 (m), 1450 (w), 1374 (w), 1269 (w), 1268 (w), 1248 (w), 1201 (w), 1159 (w), 1109 (w), 1058 (w), 1024 (w), 990 (w), 876 (w), 758 (s), 699 (w), 530 (w) cm^{-1}; (We have found that ^1H NMR peaks of this compound can be concentration dependent and can shift +/- 0.2 ppm.) **^1H NMR ($CDCl_3$, 400 MHz):** δ 7.39-7.28 (5H, m), 7.01 (2H, d, *J* = 7.2 Hz), 6.92 (1H, dd, *J* = 6.4, 6.4 Hz), 4.15 (1H, q, *J* = 5.2 Hz), 3.11 (2H, dq, *J* = 11.6, 11.6 Hz), 2.57 (4H, q, *J* = 7.6 Hz), 2.62 (3H, br s), 1.17 (6H, t, *J* = 7.6 Hz); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 145.0, 144.6, 136.7, 128.9, 127.7, 126.9, 126.6, 122.9, 57.6, 56.7, 24.6, 15.1; **HRMS (EI+):** Calcd for $C_{18}H_{25}N_2$ [M^++H]: 269.20177, Found: 269.20177; **Optical Rotation:** $[\alpha]_D^{20}$ –17.7 (*c* = 1.33, $CHCl_3$) *(This optical rotation was taken with the R enantiomer of compound **4.20** (opposite enantiomer to what is shown above))*.

(*S*)-Isobutyl 2-(2-(2,6-diethylphenylamino)-1-phenylethylamino)benzenesulfonate (4.21): To a flame-dried round bottom flask in a N_2-filled glove box were added

isobutyl-2-bromobenzenesulfonate (**4.2**) (1.10 g, 3.75 mmol), Pd_2dba_3 (0.201 g, 0.219 mmol), NaO*t*Bu (0.599 g, 6.57 mmol) and *rac*-binap (0.409 g, 0.657 mmol). The flask was fitted with a reflux condenser capped with a septum and removed from the glove box. A solution of diamine **4.20** (0.979 g, 3.75 mmol) in THF (36.5 mL) was added through a syringe and the resulting red solution was allowed to stir at 66 °C (oil bath) for 15 h. The mixture was allowed to cool to 22 °C and the reaction was quenched by the addition of a sat. aqueous solution of NH_4Cl (30 mL). The layers were separated and the aqueous layer washed with CH_2Cl_2 (50 mL x 3). The organic layers were combined, dried over Mg_2SO_4, filtered and concentrated under reduced pressure to afford a red oil. The oil was dissolved in toluene, loaded on top of a column containing silica gel, and purified by silica gel chromatography (100% petroleum ether (to elute toluene) to 90% petroleum ether /Et_2O) to afford **4.21** (1.73 g, 3.60 mmol, 98.8%) as a yellow solid (contains ~20% dehalogenated aryl sulfonate). **IR (neat)**: 3380 (br), 3063 (w), 3029 (w), 2961 (s), 2932 (m), 2864 (m), 1602 (w), 1569 (m), 1509 (w), 1459 (w), 1450 (s), 1349 (w), 1269 (w), 1222 (w), 1184 (s), 1163 (s), 1109 (w), 1062 (w), 1024 (w), 973 (s), 952 (m), 843 (m), 813 (m), 573 (w), 522 (w) cm^{-1}; (We have found that ^1H NMR peaks of this compound can be concentration dependent and can shift +/- 0.2 ppm.) **^1H NMR ($CDCl_3$, 400 MHz):** δ 7.89-7.66 (2H, m), 7.52-6.97 (7H, m), 6.78 (1H, d, *J* = 3.2 Hz), 6.63 (1H, d, *J* = 8.0 Hz), 4.74 (1H, q, *J* = 6.0 Hz), 3.84 (1H, dd, *J* = 9.6, 6.4 Hz), 3.79 (1H, dd, *J* = 9.6, 6.8 Hz), 3.38 (1H, dd, *J* = 11.6, 4.4 Hz), 3.21 (1H, dd, *J* = 12.0, 6.0 Hz), 2.54 (2H, q, *J* = 7.6 Hz), 2.44 (2H, q, *J* = 7.6 Hz), 1.98 (1H, s, *J* = 6.8 Hz), 1.11 (6H, t, *J* = 7.6 Hz), 0.94 (3H, d, *J* = 3.2 Hz), 0.92 (3H, d, *J* = 3.6 Hz); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 146.0,

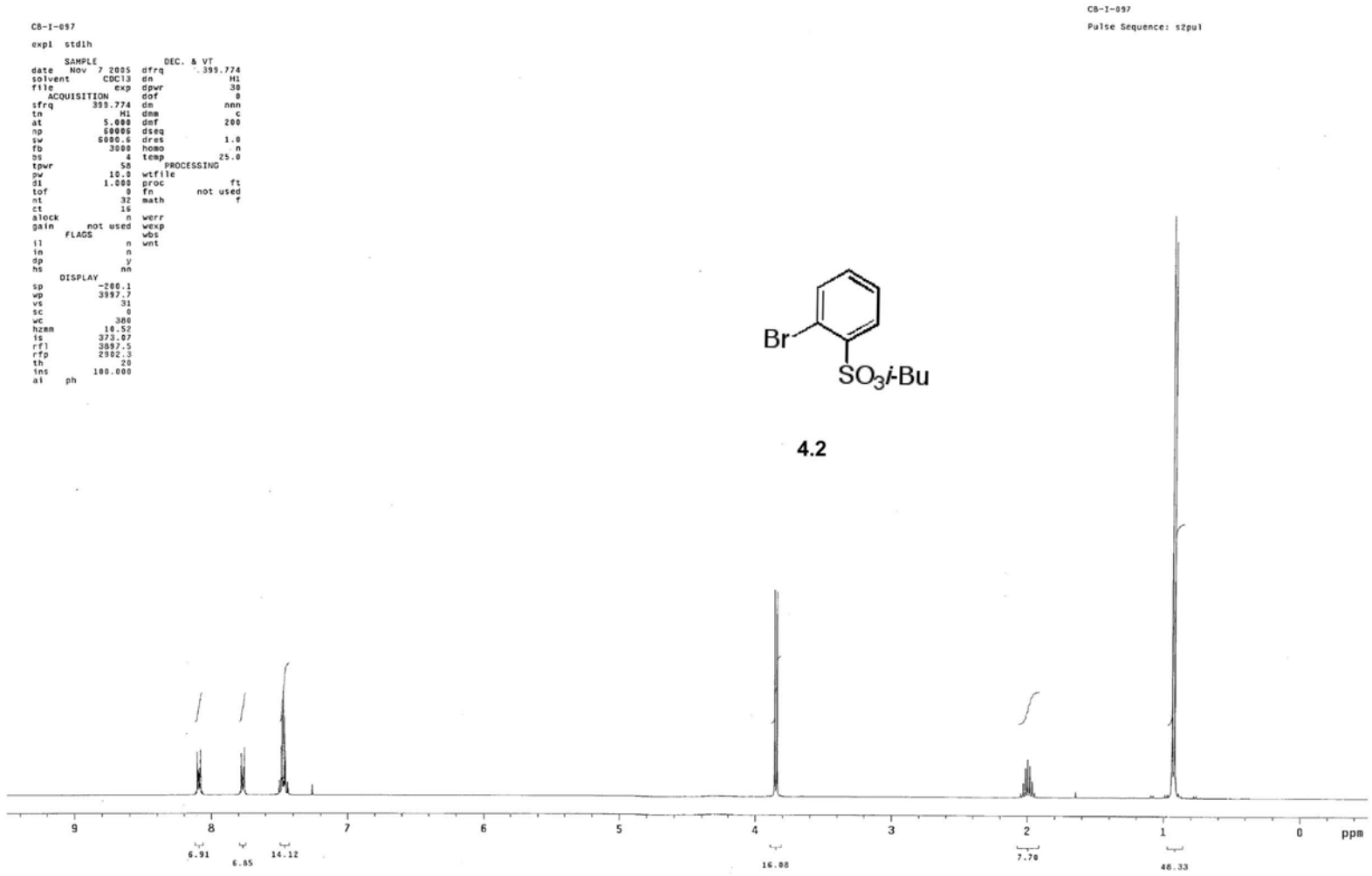
143.9, 140.3, 137.7, 135.4, 131.0, 129.2, 128.3, 128.1, 126.8, 126.6, 123.8, 115.9, 113.8, 76.5, 57.7, 56.2, 28.3, 24.2, 18.9, 15.1; **HRMS (EI+):** Calcd for $C_{28}H_{37}N_2O_3S$ [M^++H]: 481.25249, Found: 481.25291; **Optical Rotation:** $[\alpha]_D^{20}$ –13 (*c* 0.95, $CHCl_3$).

Imidazolinium Salt V: Diamine **4.21** (4.66 g, 9.71 mmol) and *N*-methyl-*N*-methylideneiminium iodide (8.98 g, 48.5 mmol, Eschenmoser's salt) were weighed out into a 75 mL heavy wall sealed tube. Acetic acid (1.04 mL, 145 mmol) was added, the vessel sealed, and the mixture allowed to stir at 110 °C (the yellow heterogeneous mixture becomes black and homogeneous upon heating). After 1 h, the mixture was allowed to cool to 22 °C and diluted with Et_2O (5 mL) and water (5 mL). The resulting mixture was basified by the *slow* addition of a saturated aqueous solution of K_2CO_3 until gas evolution ceased. Dichloromethane (10 mL) was added and the aqueous layer separated. The aqueous layer was washed further with CH_2Cl_2 (2 × 10 mL) and the combined organic layers dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a yellow solid. The yellow solid was purified by silica gel column chromatography (100% EtOAc to 2% MeOH/EtOAc to 5% MeOH/EtOAc) to afford imidazolinium salt **V** (2.10 g, 4.83 mmol, 50.0%) as a white solid. (Note: Separation of a yellow impurity by silica gel column chromatography can often be tedious. This solid can be obtained in white crystalline form by recrystallization from CH_2Cl_2:Et_2O, but is not required for effective formation of **Ag-V**.) **m.p.:** 251-252 °C; **IR (neat):** 3051 (m), 2965 (w), 2933 (m), 2874 (w), 1612 (w), 1583 (w), 1457 (m), 1430 (m), 1310 (w), 1282 (w), 1266 (w), 1236 (w), 1200 (m), 1139 (m), 1091 (w), 1054 (w), 1021 (w), 956 (w),

890 (w), 865 (w), 806 (w), 758 (s), 735 (w), 717 (w), 704 (s), 684 (w), 650 (m), 612 (m), 580 (m), 565 (m), 538 (w), 523 (w), 492 (w), 446 (m), 427 (w), 405 (m) cm^{-1}; (We have found that ^1H NMR peaks of this compound can be concentration dependent and can shift +/- 0.2 ppm.) **^1H NMR ($CDCl_3$, 400 MHz):** δ 8.64 (1H, s), 8.19 (1H, dd, *J* = 8.0, 1.2 Hz), 7.49-7.45 (5H, m), 7.43 (1H, t, *J* = 7.6 Hz), 7.34 (1H, dt, *J* = 7.6, 1.2 Hz), 7.31-7.21 (2H, m), 7.10 (1H, dt, *J* = 7.2, 1.2 Hz), 6.61 (1H, dd, *J* = 7.6, 0.8 Hz), 6.25 (1H, dd, *J* = 12.4, 9.6 Hz), 4.86 (1H, t, *J* = 12.0 Hz), 4.16 (1H, dd, *J* = 11.6, 9.2 Hz), 3.11 (1H, dq, *J* = 7.6, 7.2 Hz), 2.98 (1H, dq, *J* = 7.2, 7.2 Hz), 2.89-2.73 (2H, m), 1.37 (3H, t, *J* = 7.6 Hz), 1.34 (3H, t, *J* = 7.2 Hz); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 159.9, 144.3, 143.6, 140.8, 136.1, 131.6, 131.2, 130.8, 130.4, 130.2, 130.0, 129.9, 128.6, 127.9, 127.2, 127.1, 68.6, 60.4, 24.5, 23.8, 15.7, 15.1; **HRMS (ESI+):** Calcd for $C_{25}H_{27}N_2O_3S$ $[M^+ + H]$: 435.17424, Found: 435.17319; **Optical Rotation:** $[\alpha]_D^{20}$ –130 (*c* 0.65, $CHCl_3$).

Ag-V: Imidazolium salt **V** (100 mg, 0.201 mmol), Ag_2O (93.0 mg, 0.400 mmol) and oven-dried <5 micron 4Å molecular sieves (ca. 50 mg) were weighed out into an oven-dried 10 mL round bottom flask fitted with a reflux condenser, and wrapped with aluminum foil. Tetrahydrofuran (1.0 mL) followed immediately by benzene (1.0 mL) were added through a syringe resulting in a black heterogeneous mixture, which was allowed to stir at 80 °C. After 2 h, the mixture was allowed to cool to 22 °C and filtered through a short plug of Celite 545 (4 x 1 cm) eluted with EtOAc (ca. 20 mL). The solution was concentrated in vacuo to afford 119 mg (0.197 mmol, 98.0%) of Ag

complex **Ag-V** as a white solid, which was stored under low light conditions. (Note: This material was obtained in crystalline form by recrystallization from CH_2Cl_2:Et_2O bilayer, but recrystallization is not required for effective Cu-catalyzed ACA.) **m.p.:** 167-170 ^oC **(**dec.); **IR (neat):** 3443 (br), 3062 (w), 2964 (m), 2928 (m), 2871 (w), 1769 (w), 1625 (w), 1590 (w), 1573 (w), 1480 (w), 1467 (w), 1443 (s), 1373 (w), 1272 (s), 1228 (w), 1198 (s), 1167 (w), 1136 (s), 1089 (w), 1053 (w), 1020 (s), 905 (w), 869 (w), 804 (w), 757 (w), 726 (w), 699 (s), 661 (s), 608 (s), 564 (s), 548 (m), 466 (w), 407 (w) cm $^{-1}$; (We have found that ^{1}H NMR peaks of this compound can be concentration dependent and can shift +/- 0.2 ppm.) **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.97 (1H, br s), 7.27-7.18 (6H, m), 7.05 (2H, d, *J* = 8.0 Hz), 6.86 (1H, br s), 6.73 (1H, br s), 6.23-6.16 (2H, m), 4.34 (1H, t, *J* = 7.2 Hz), 3.71 (1H, t, *J* = 8.4 Hz), 2.62-2.28 (4H, m), 1.28 (3H, t, *J* = 7.2 Hz), 0.94 (3H, t, *J* = 7.2 Hz); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 207.7, 205.8, 143.5, 143.3, 141.4, 139.4, 136.8, 135.5, 130.7, 130.6, 130.6, 129.5, 129.0, 128.7, 128.6, 128.3, 127.8, 126.3, 68.4, 61.5, 24.7, 23.5, 15.9, 15.5; **HRMS (EI+):** Calcd for $C_{25}H_{25}N_2O_3NaSAg$ [M^++Na]: 563.0535, Found: 563.0536; **Optical Rotation:** $[\alpha]_D^{20}$ –64 (*c* 0.82, $CHCl_3$) *(This optical rotation was taken with the R enantiomer of compound **Ag-V** (opposite enantiomer to what is shown above))*.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th 20
ins 100.000
al ph
DEC. & VT
dfrq 399.774
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dpwr 38
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
temp 25.0
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fn not used
math f
werr
wexp
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CB-I-097
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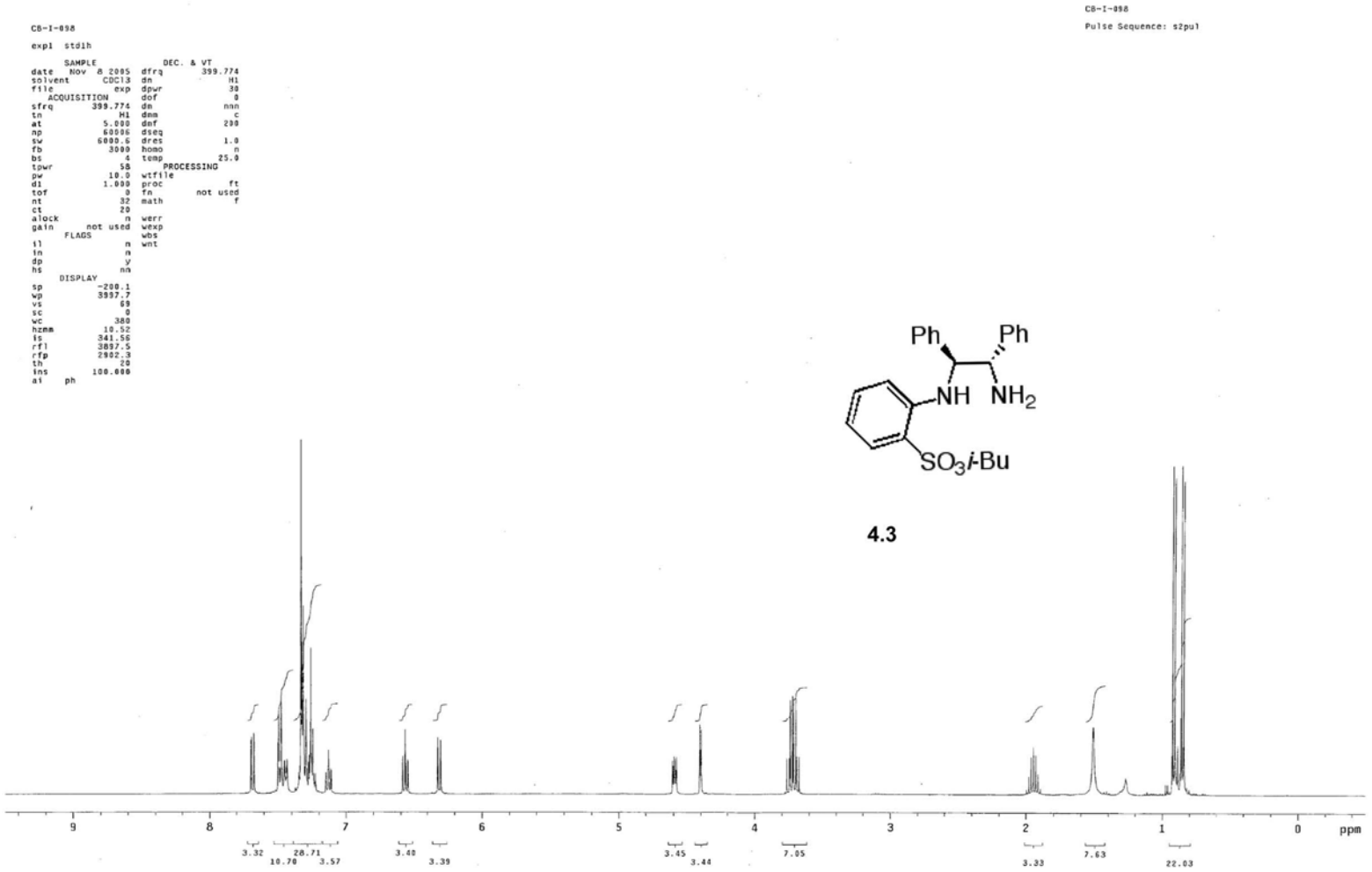
Br
SO3i-Bu
4.2
9
8
7
6
5
4
3
2
1
0
ppm
6.91
6.85
14.12
16.08
7.70
48.33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sw 6000.6
fb 3000
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tpwr 58
pw 10.0
d1 1.000
tof 0
nt 32
ct 20
alock n
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hs nn
DISPLAY
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vs 69
sc 0
wc 380
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ks 341.56
rfl 3897.5
rfp 2902.3
th 20
ins 100.000
ai ph
DEC. & VT
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dpwr 38
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
temp 25.0
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math f
werr
wexp
wbs
wnt
C8-I-098
Pulse Sequence: s2pul
Ph
Ph
NH
NH2
SO3i-Bu
4.3
9
8
7
6
5
4
3
2
1
0
ppm
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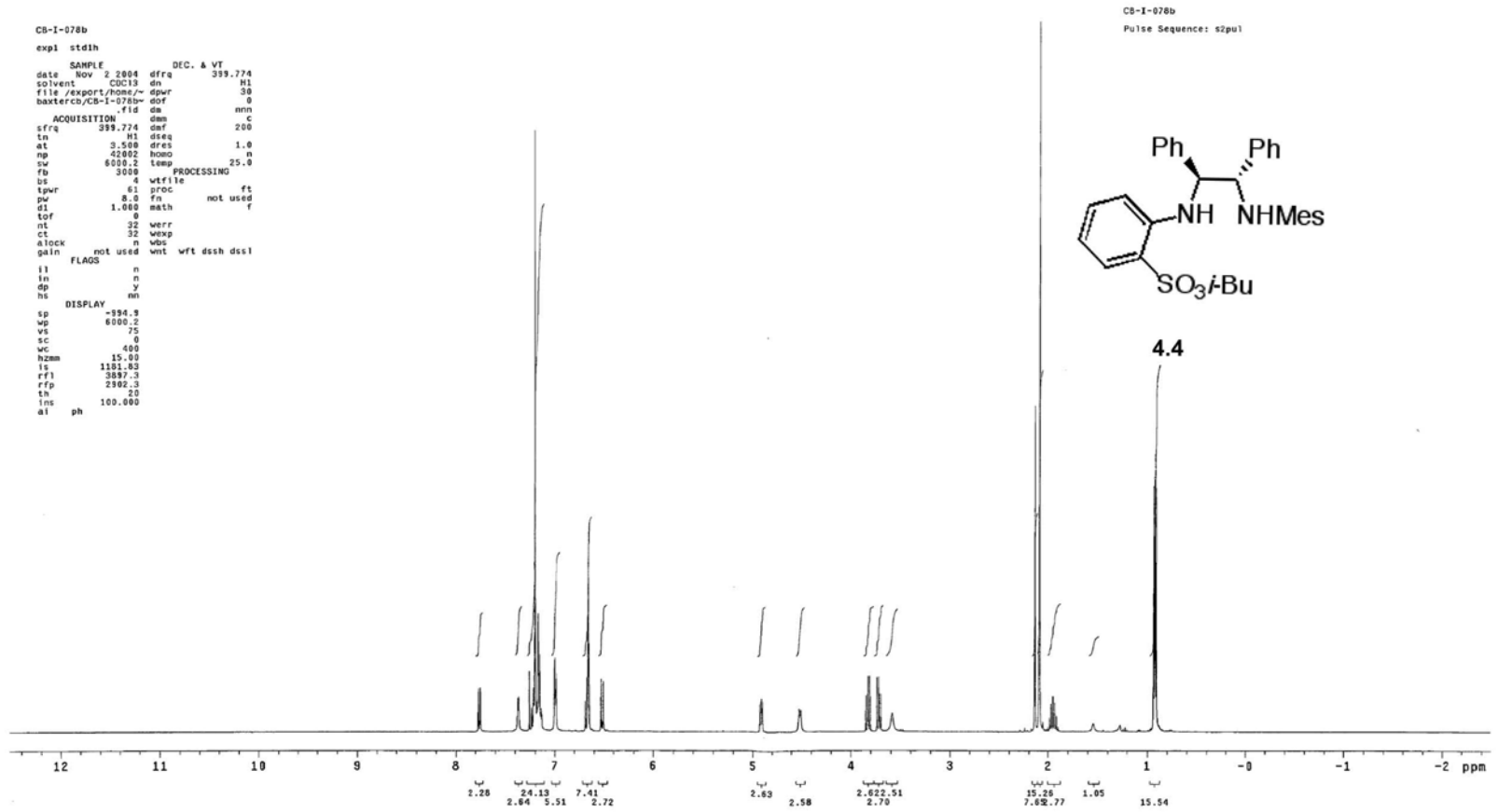
3.57
3.40
3.39
3.45
3.44
7.05
3.33
7.63
22.03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hs nn
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rfp 2902.3
th 20
ins 100.000
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dmm c
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dseq
dres 1.0
homo n
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werr
wexp
wbs
wnt wft dssh dssl
CB-I-078b
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Ph
Ph
NH
NHMes
SO3i-Bu
4.4
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
-2 ppm
2.28
24.13
2.64
5.51
7.41
2.72
2.63
2.58
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15.26
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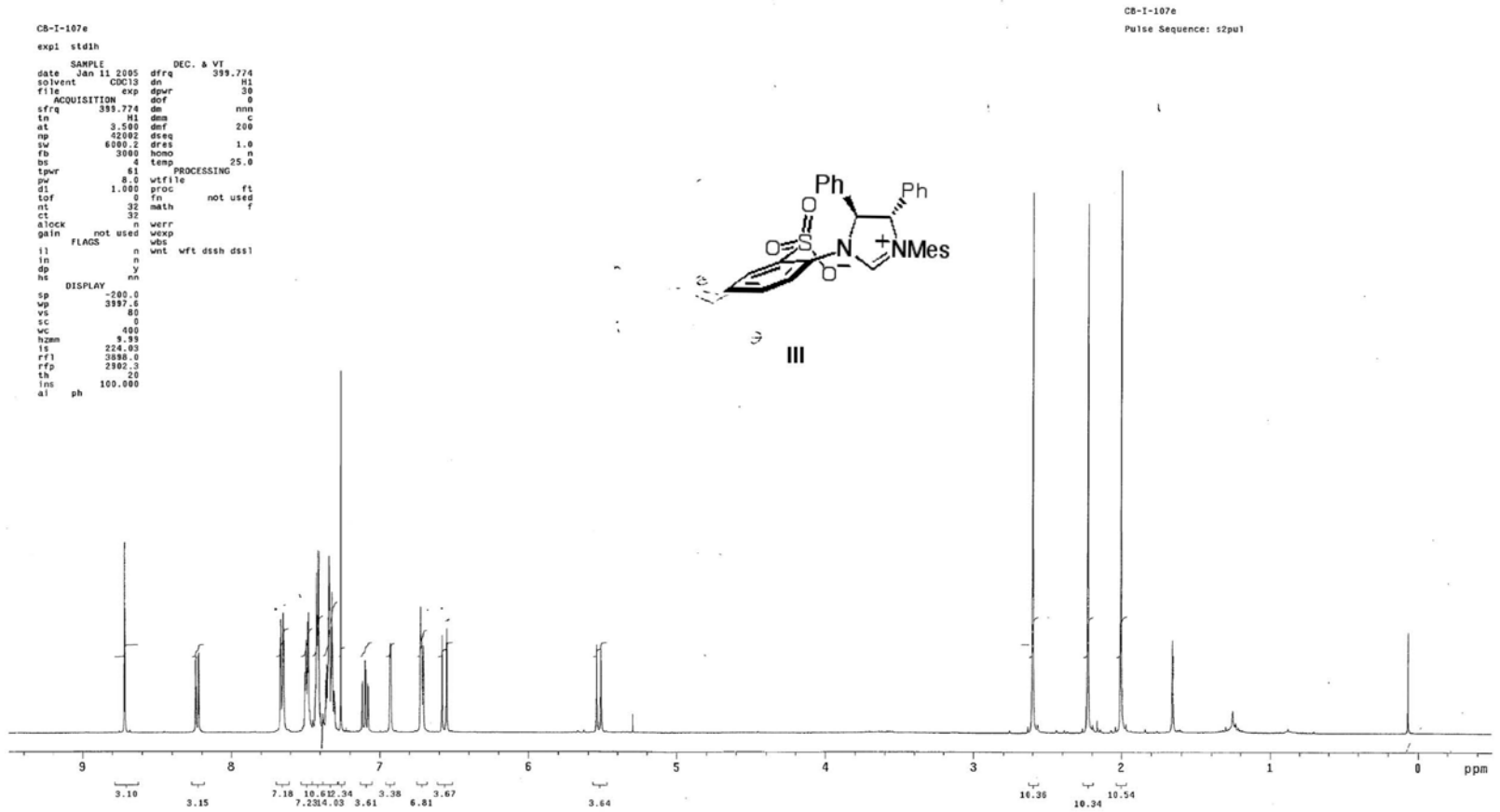
1.05
15.54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sc 0
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th 20
ins 100.000
ai ph
DEC. & VT
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dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
temp 25.0
PROCESSING
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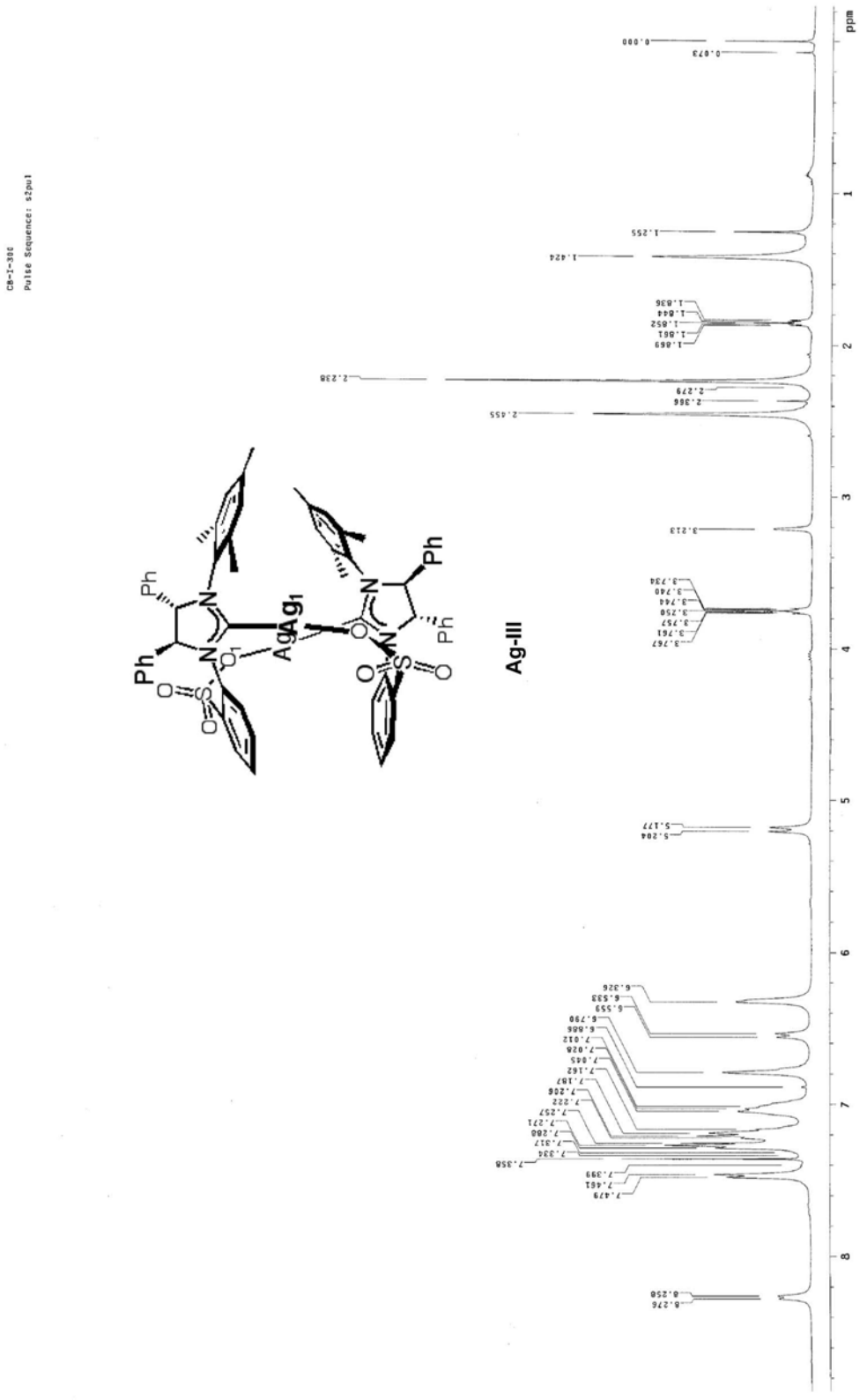
proc ft
fn not used
math f
werr
wexp
wbs
wnt wft dssh dssl
CB-I-107e
Pulse Sequence: s2pul
Ph
Ph
O
O
S
N
+NMes
O−
III
9
8
7
6
5
4
3
2
1
0
ppm
3.10
3.15
7.18
10.61
2.34
7.23
4.03
3.61
3.38
6.81
3.67
3.64
16.36
10.34
10.54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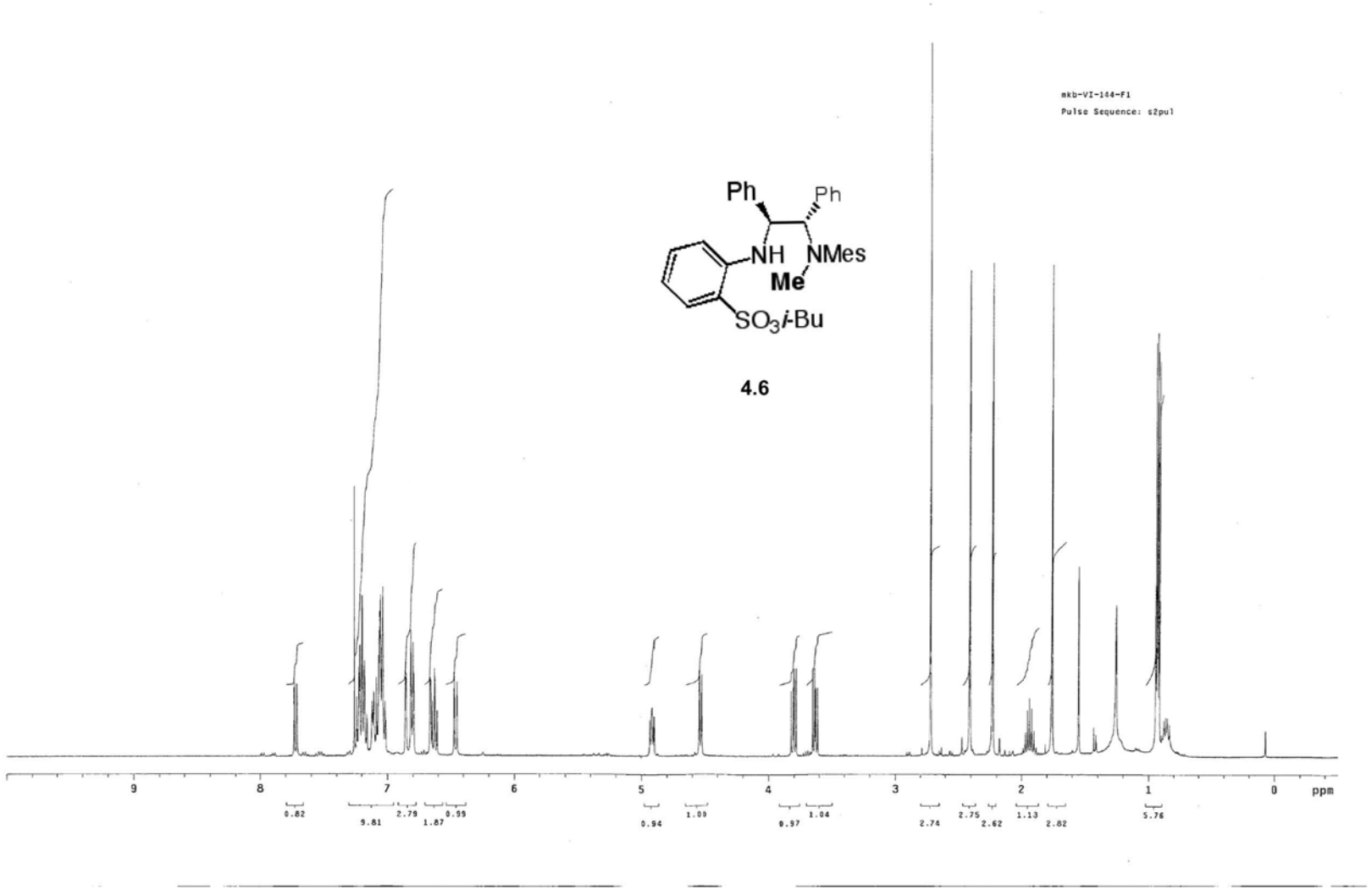
Ph
Ag
Ag
Ph
Ph
Ag-III
ppm

Ph
NMes
Ph
N
O
S
O
O
t-Bu
4.5
ppm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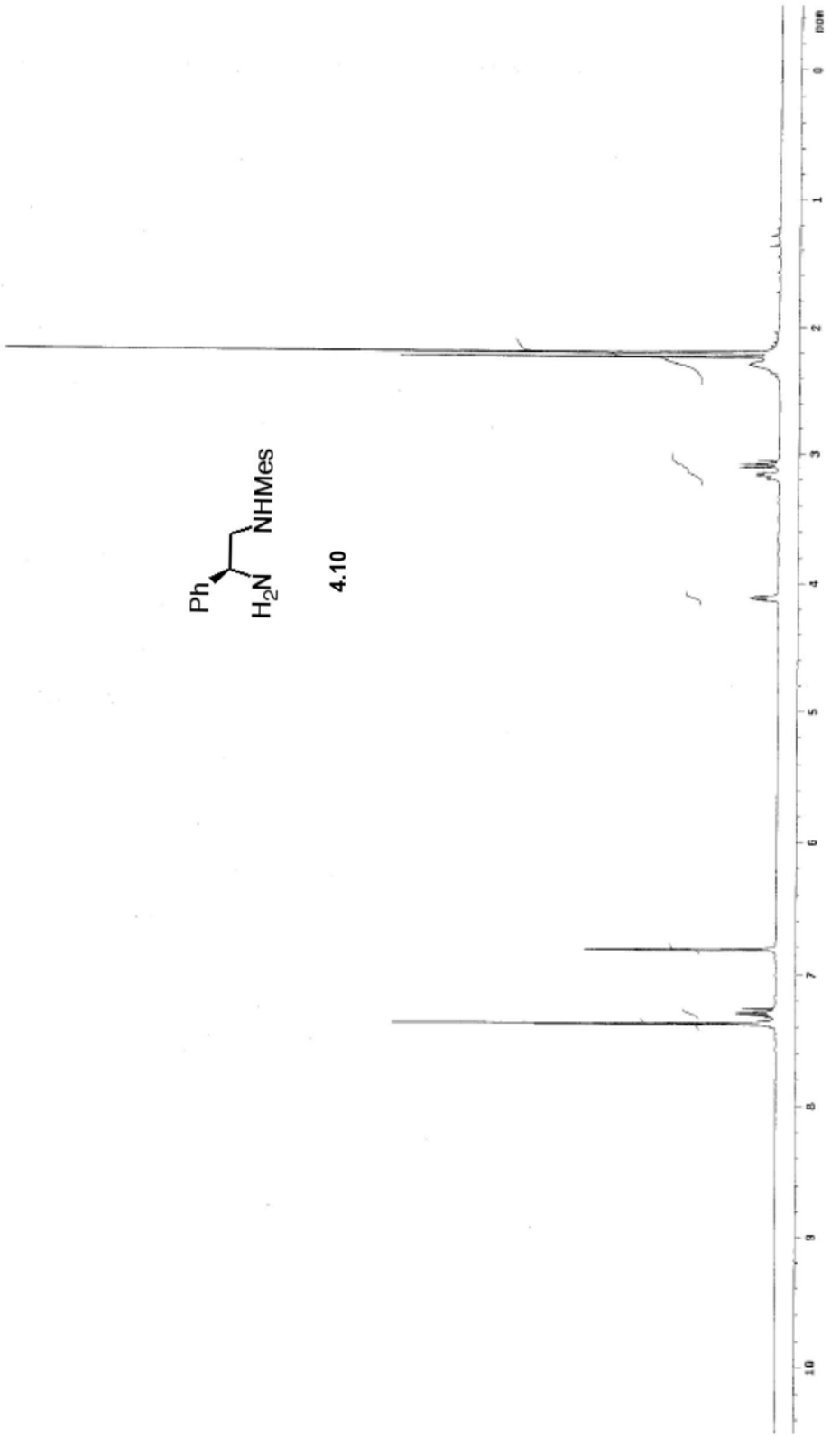
Ph
NH
NMes
Me
SO3i-Bu
4.6
9
8
7
6
5
4
3
2
1
0
ppm
0.82
9.81
2.79
1.87
0.99
0.94
1.09
0.97
1.04
2.74
2.75
2.62
1.13
2.82
5.76

Ph
t-Bu
S
NH
O
NMes
Boc
4.15
ppm


Ph
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NHMes
4.10

Ph
NH
NHMes
SO3t-Bu
4.11
ppm

Ph
NMes
IV
ppm

Ag-IV
ppm

Ph
BocN
O
S
O
O
4.19
1
2
3
4
5
6
7
8
9
10

Et
HN
Et
Ph
H2N
4.20
1
2
3
4
5
6
7
8
9
10

Et
Et
NH HN
Ph
SO3i-Bu
4.21
1
2
3
4
5
6
7
8
9
10

Ph
O
S
O
N
+N
Et
Et
v
10
9
8
7
6
5
4
3
2
1

Ag-V